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Laboratory Medicine in Healthcare

Gurmukh Singh, MD, PhD, MBA*

Abstract

Laboratory medicine provides essential information that drives 70% of clinical decisions. Interpretation of patient results requires comparison with normal values/reference ranges. Normal values vary by age, gender, ethnicity, and testing methods. Finding "healthy" individuals to ascertain normal values is an intractable issue, further complicated by the general practice of using the central 95% of values. Matters are made more difficult by the observation of a paradox between medically prescribed ranges and optimal ranges based on longevity data. Reporting of laboratory results on patient portals may cause unwarranted concern due to minor differences in a patient's results from "normal" values. Reducing the spread of normal values warrants developing reference ranges specific for age, gender, ethnicity, geographic area and methods of testing. Using minimally necessary levels of essential trace nutrients versus optimal levels is a source of confusion in determining normal values. In addition to reporting the raw results on patient portal a brief interpretation addressing the importance of variation from normal values should be included to avoid unwarranted concerns by patients. Judicious use of laboratory testing is important for not only cost controls but also to avoid incurring additional clinically meaningless variations from normal values due to increased volume of tests.

Keywords: Laboratory Medicine; Reference ranges; Essential Nutrients; Cost of Laboratory Testing; Harmonization

Abbreviations: 2, 3 DPG: 2,3-diphosphoglycerate; HIV: Human Immunodeficiency Virus; EBV: Epstein Barr Virus; WHO: World Health Organization; CDC: Centers for Disease Control and Prevention; CMS: Centers for Medicare and Medicaid Services; LDL: Low Density Lipoprotein; HDL: High Density Lipoprotein; BMI: Body Mass Index; PSA: Prostate Specific Antigen; MGUS: Monoclonal Gammopathy of Undetermined Significance; SFLC: Serum Free Light Chains; RDA: Recommended Daily Allowance; FDA: Food and Drug Agency; GDP: Gross Domestic Product; CMP: Comprehensive Metabolic Profile; TSH: Thyroid Stimulating Hormone

Introduction

Healthcare at the patient doctor interface involves multiple issues with each having its own importance, relevance and salience. History taking and physical examination remain the key first steps in arriving at a diagnosis and establishing doctor patient rapport and trust building. Doctor patient encounters often require testing body fluids, tissues and imaging studies. It is generally accepted that laboratory testing drives about 70% of the clinical decisions, thus, Laboratory Medicine has an essential albeit a contributory/supportive role in healthcare [1]. The main product and contribution of Laboratory Medicine to healthcare is testing body fluids and tissues for accurate diagnoses and providing blood and blood components for transfusion.

Affiliation:
Shepeard Chair in Clinical Pathology, Medical College of Georgia at Augusta University, 1120 15th Street. Augusta. GA. 30912, USA

***Corresponding author:**
Gurmukh Singh, Shepeard Chair in Clinical Pathology, Medical College of Georgia at Augusta University, 1120 15th Street. Augusta. GA. 30912, USA.

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There are five key reasons for performing laboratory tests. As a corollary, a good laboratory test should fulfill at least one of these roles [2]. The five types of tests and examples of each are presented below:

1. Detecting a disease or a predisposition to disease: An elevated blood sugar level of greater than 200 mg/dL on routine testing points to the diagnosis of diabetes in the patient [3]. An elevated blood cholesterol indicates a predisposition to heart disease [4]
2. Confirm or reject a diagnosis: A breast biopsy showing cancer will confirm the diagnosis of breast carcinoma; detection of human immunodeficiency virus RNA in blood will confirm a diagnosis of HIV. Lack of HLA-DQ 2 and 8 will essentially rule out a diagnosis of Celiac disease in a person with gastro-intestinal symptoms [5]
3. Establish prognosis: Morphological and nucleic acid characteristics of tumors point to the likely course of the tumor and response to treatment. Higher levels of free monoclonal free light chains portend shorter survival in a patient with multiple myeloma [6-10]. High level of hematocrit in a person presenting with pancreatitis suggests poorer outcome [11]
4. Guide patient management: Presence of ketoacidosis indicates a certain treatment in a patient with diabetes, treatments for lymphoid tumors and leukemias are dictated by the morphologic and molecular characteristic of the tumor cells, nutritional deficiencies of specific agents diagnosed by laboratory tests guide appropriate replacement therapy [12]
5. Monitor the efficacy of treatment: Monitoring the anion gap provides information about the response to the treatment of keto-acidosis, decline in serum levels of monoclonal immunoglobulins indicates response to therapy in multiple myeloma, rise in hemoglobin levels in an anemic subject indicates appropriate supplementation of nutritional elements [13]

Laboratory results often have numerical values, e.g., hemoglobin level in grams per deciliter, plasma glucose level in milligrams per deciliter, vitamin D levels in nanograms per milliliter etc. However, other results are words, phrases or sentences that may also have numbers, e.g., blood group may be A, B, AB, or O; urine culture result may state E. coli at greater than 100,000 organisms per ml; tissue biopsy may state adenocarcinoma of the lung, cirrhosis of liver, malignant melanoma of skin etc. It is worth noting that most countries use metric measures/numbers/units that often have markedly different values, e.g., what is plasma glucose level of 126 mg/dL in USA would be expressed as 7.0 mmol/L in Canada [14,15]. Only USA and two other "illustrious" counties of Liberia and Myanmar (Burma) still use the non-metric units.

In this communication the focus is on testing of body fluids. Tissue and cellular examinations are a different discipline and are handled in the divisions of Anatomic and Molecular Pathology and are not addressed here.

Normal Values/Reference Ranges

For each analyte/chemical/cell type there are certain values that are seen in individuals without health problems. However, defining a normal, healthy person has its own issues. The World Health Organization (WHO) adopted the following definition of health in 1948: "**Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity**." The search for a healthy person is likely to face the same odds as one for finding a "happy" person in the poem, "The enchanted shirt" by John Hay. In a lighter vein, an intern's definition of a healthy person, **"Someone who has not been investigated enough"** is just as appropriate.

In practice, a person without an obvious illness of the organ system affected by the analyte or affecting the analyte is generally considered healthy. Blood donors are the usual surrogates for healthy people [16]. At one time, metabolic units in academic medical centers admitted "healthy" people who were maintained on a prescribed diet and physical activity. Blood or other body fluids were collected in the recumbent, post absorptive state, usually on waking up in the morning, and analyzed for substances of interest with gold standard analytical methods and the results were used as the normal values/reference ranges. Real life specimen collection and testing add a number of variables to the results as compared to the ideal, e.g., an ambulatory person will have higher levels of skeletal muscle enzymes, a "social" drinker will have higher liver enzyme levels, a person with inadequate hydration may higher blood levels of urea etc [17,18]. A person presenting for a glucose tolerance test is expected to have been on a diet containing at least 150 gm of carbohydrates/day for three days prior to the test and be in a fasting state for at least 8-hours [19]. Compliance with such requirements is seldom adequate. Collection of 24-hour urine is usually fraught with errors in the volume collected and the use of proper preservatives.

The College of American Pathologists recommends that each laboratory establish its own reference ranges for the tests it performs using samples from the population served by the laboratory. The classical requirement is to test a minimum of 120 "healthy" people, called a partition, of each age, gender, ethnic or other characteristics to obtain a baseline. (This is an impractical requirement and work arounds are generally acceptable). In the usual process the results are plotted and the lowest 2.5% and highest 2.5% of the values are discarded and the central 95% is used as the reference range [20]. By using this method, 5% of normal people will have an

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abnormal result. Or if 20 different tests are done on a healthy person at least one test will likely display abnormal values. A more accurate statistic alternative is that the probability of no abnormal test result in a healthy subject, in a panel of 20 tests is (0.95)*20=0.358. Thus, (1-0.358=0.642), 64.2% of "normal" patients will have at least one "abnormal" test result in a panel of 20 tests. For this and other reasons, laboratory tests should be ordered only if an abnormality is expected from other clinical data. The built-in 5% error rate demands repeat testing, additional testing, imaging studies and induces unwarranted patient stress and financial toxicity. The more tests are done, the higher the risk of false positive results. An amusing quote by Dr. Catherine D DeAngelis reads, "Remember, ordering a diagnostic test is like picking your nose in public: you must first consider what you will do if you find something" [21,22].

Variations on the Central 95% Theme

In some instances, an expert opinion is overlaid on the central 95% of population values. For example, the recommended reference ranges for blood cholesterol and LDL are lower than those observed in the general population, similar to the adjustments to blood pressure and BMI values. In the case of troponin, the highest 99th percentile is taken as the normal upper limit of the reference range, there being no normal lower limit. In other cases, the high and low values have different connotations, e.g., high serum creatinine indicates renal insufficiency, however low creatinine is not a marker of renal hyperfunction but is an indication of sarcopenia [22].

Patient Portal for Test Results

Federal regulations require that laboratory results, on confirmation of the results, be released to patients. This requirement has altered the process of doctor patient interaction. Minor variations in laboratory test results that are labeled by the laboratory as low/high/abnormal may cause unwarranted worry to the patients. The number of laboratory results that are outside the "normal range" far exceeds the clinically meaningful abnormal results due to disease [22,23].

The results from usually accepted technique for ascertaining "normal values"/reference ranges are affected by variations in methods of testing at different laboratories, variations due to age, gender, ethnicity, seasonality, and random variations. It is not generally appreciated that the normal values reported by the testing laboratory are not a gold standard but derived through a process with many assumptions, differences in methods, overlay of expert opinion and other sources of variation in values [22].

From my experience of addressing questions on HealthTap, more than 20% of the questions by patients are about laboratory test results. Many of these questions are prompted by minor variation from reference values. Therefore, in addition to reporting normal values along with patient results, we should consider including clinical significance of the findings, in simple terms, such as, no immediate concern, warrants discussion with doctor at the next visit, or recommend contacting your doctor for further action [22].

Additional factors Affecting Reference Ranges

As alluded to earlier, reference ranges specific for different age groups, genders, ethnic populations and geographic areas may need to be developed. Examples for each of these situations are given below:

Age: Hemoglobin level of 12.0 g/dL is normal for an adult female but would be considered abnormally low in a newborn girl. With the decline in fetal hemoglobin and increase in the adult type of hemoglobin, the levels normalize to the adult levels over a few months. A similar change is noted over a longer time frame in serum immunoglobulin levels. Hormone levels, especially sex hormone levels vary by age, menstrual cycle and pregnancy. Serum alkaline phosphatase levels are higher in growing children and pregnant women, driven by the bone growth in children and fetus [24].

The reference range for prostate specific antigen (PSA) derived from an under 40-year-old population is not applicable to senior citizens. Age specific reference ranges for PSA have been developed but the ranges still do not provide a clear-cut demarcation between normal, hyperplastic/hypertrophied prostate and prostate cancer [25].

In addition to the biological effects of age, presence of other pathologies in older subjects, affect the value of reference ranges developed from "healthy" adults. A cogent example of this issue is the misuse of serum free immunoglobulin light chain assay (SFLCA). The reference range for serum free kappa and lambda light chains were derived from blood donors and healthy residents of Olmstead County, Minnesota, USA. The reference range of kappa/lambda ratio of 0.26 to 1.65, derived from this study, has been found to have too many exceptions for it to be useful. Initially, individuals with serum free light chain kappa/lambda ratio outside this range were labeled as having monoclonal gammopathy of undetermined significance (MGUS). It is noteworthy that the MGUS diagnosis was made without demonstrating any monoclonal protein or lesion. Later on, it was discovered that tertiary care patients, without any monoclonal gammopathy, had a 36% prevalence of an abnormal kappa/lambda ratio [26,27]. In addition, about 30% of patients with a detectable monoclonal immunoglobulin in serum had a normal kappa/lambda ratio. Given that an abnormal kappa/lambda ratio is not diagnostic of monoclonal gammopathy and a normal ratio does not exclude monoclonal gammopathy, the role of SFLCA is more or less limited to monitoring light chain

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myelomas and diagnosing light chain predominant multiple myelomas. Even the revision to the upper limit of normal range to 3.1, from 1.65 produces more than 80% false positive results. In an older population, the presence of lesions with chronic inflammation causes an increase in serum free light chains, especially an increase in kappa free light chains [28]. Monoclonal light chains are pathogenic but elevated levels of polyclonal free light chains indicate chronic lesions, especially inflammatory lesions, as in the case of elevated Erythrocyte Sedimentation Rate, elevated C-reactive protein, and elevated serum ferritin [28,29].

Gender: In addition to the sex hormone levels, differences in hemoglobin levels among men and women is the most prominent gender-based issue in common laboratory test results. Adult women have about 2.0 g/dL lower levels of hemoglobin than men yet manage to deliver sufficient oxygen to their tissues. The lower hemoglobin level in women is unlikely to be due to menstrual blood loss or iron deficiency, though both of these factors are in play. Estrogen driven higher levels of 2-3 DPG facilitate release of oxygen from hemoglobin enabling women to deliver adequate amount of oxygen to tissues with 2.0 gm lower hemoglobin than men. This hypothesis is supported by the lower hemoglobin levels in transwomen who do not menstruate, though loss of testosterone may be a factor, however, estrogen administration affecting 2-3 DPG values may be more important [22]. Genetic variations in the globin part of hemoglobin may induce higher or lower oxygen affinity for hemoglobin. Patients with variations that reduce the oxygen affinity of hemoglobin have lower levels of hemoglobin without any ill effects that may be expected from "anemia". Patients with variant hemoglobin that binds oxygen more tightly have higher levels of hemoglobin, just as the higher affinity of fetal hemoglobin results in higher hemoglobin levels in the fetus and newborn. Of the common laboratory tests, one other notable feature of gender difference is the higher levels of HDL in women than in men [30].

Reliable reference ranges for transgender and non-binary people have not been worked out in detail, in part due to the variations induced in the types and amounts of hormones and surgical procedures used in gender affirming care [30].

Physiological state: Physiological changes during pregnancy and climacteric, while only relevant to women, are important issues due to lack of detailed information about "normal" values in these times of transitional states. A similar issue may apply to developing fetus, though fetal testing is not a routine occurrence [30].

Testing a blastocyst before implantation is an important procedure in avoiding genetic disorders, e.g., sickle cell disease, cystic fibrosis, Lesch Nyan Syndrome etc. in the potential human. Embryo selection is a controversial procedure; however, knowledge of this testing is critical for optimal healthcare [30].

Ethnicity: There is current emphasis on removing "race" from consideration in healthcare due in part to past practices of discrimination in healthcare based on race/ethnicity. This extends to developing race neutral reference ranges. One recent example of the race neutral philosophy is the revision to the equation for calculating estimated glomerular filtration rate, by removing race as a factor [31]. Review of common laboratory test results from National Health and Nutrition Examination Survey did not reveal meaningful differences among races in the USA [32]. Standard textbooks describe normal values for age and sex but do not include values specific for race/ethnicity.

However, ethnicity matters in healthcare. Just compare the average height of people in the Netherlands versus East Timor! The average height of men in the Netherlands is 6.0 feet as compared to 5 feet 2.9 inches in East Timor/Timor Leste [33]. The differences are likely to be multifactorial but are real. The common refrain being that race is a social construct and is not based on biology. It is often cited that there are more DNA differences in the genome within a population than among populations [34,35]. Be that as it may, try telling that to someone with sickle cell disease. This disorder is driven by the difference in one nucleotide base-pair out of three billion! Many other hemoglobin disorders are also single nucleotide driven. The genetic variation in Sickle cell disease is not race driven but is common in areas with high incidence of falciparum malaria. However, it applies predominantly to Africa and a part of Eastern India. There is a similar geographic and ethnic variation in other hemoglobinopathies as well. Hemoglobin E disorder is commoner in East Asia. Beta Thalassemia being more prevalent in Mediterranean and middle eastern countries and alpha thalassemia being a more prevalent disorder in East Asia [36]. As in the case of hemoglobin variations/disorders, many other differences among various peoples are genetically/DNA driven while others may be related to cultural practices or a combination of multiple factors. In multigenic disorders, it may not be feasible to disentangle genetic and cultural matters. A few examples of each of these factors are presented below:

Leukocyte count and A1c levels in Blacks: In a proportion of people of African descent their baseline neutrophil count is low enough to be called neutropenia when compared to the white population [37]. This anomaly/variation is not pathological nor race driven but an indication of the Duffy null status of the individual. It is important to recognize this to avoid invasive investigations in a black child or adult with apparent neutropenia. As in the case of Hb S gene, lack of Duff blood group is protective against malaria and provided a survival advantage to the individuals with this variation [38]. However, Duffy null status is also associated

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with other changes in blood parameters, the most prominent being low neutrophil count. Hb A1c levels are higher in people of African descent, despite being normoglycemic [39]. However, people with sickle cell trait have lower A1c levels for plasma glucose levels similar to those in other populations [39,40].

Bombay phenotype: In rare individuals with ABO null genetic state, they type as blood group O but have antibodies to red cells from all other blood group including O, A, B and AB individuals, thus making is almost impossible to find compatible blood for the individual. Only another person with Bombay phenotype could be a donor for a person with ABO null status, i.e., Bombay phenotype [41,42]. The ABO null genotype results in lack of H substance, on red cells, that is the precursor material for blood groups O, A, and B antigens. Lack of H substance results in the person making alloantibodies to O, A, B and AB blood group antigens, just as blood group A people make antibodies to blood group B antigen. Bombay phenotype is almost exclusively seen in Gujrat province in India.

Vitamin D reference range: People of African descent have lower serum levels of 25(OH) vitamin D while having better bone mineral density. This is explained by the genetically determined lower levels of vitamin D binding protein resulting in lower total vitamin D levels while the bioavailable vitamin D is normal. Thus, the reference range for vitamin D levels, derived from white population is not application to black individuals [43]. The low levels of vitamin D in African Muslim women are, in part, due to extensive covering by clothes and limited opportunities outdoors and exposure to sunlight.

The higher incidence of many disorders, e.g., hypertension, heart disease, multiple myeloma, and lower life span among people of African descent in the USA probably reflect multiple genetic, and cultural issues, but nevertheless warrant consideration in healthcare [44-48].

IgA and Haptoglobin deficiencies: IgA deficiency and deficiency of haptoglobin are related to allergic reactions on blood transfusion. A person with IgA or haptoglobin deficiency may make antibodies to these proteins and suffer similar allergic reactions on blood transfusion. There is marked ethnic variability in the prevalence of these deficiencies. Haptoglobin deficiency being commoner in Japanese and IgA deficiency being more common among whites [49,50].

Alcohol metabolism: Deficiency of acetyl aldehyde dehydrogenase is common in East Asian individuals to the extent that nearly a quarter of the people of East Asian descent are affected. Mutation in the ALDH2 gene, resulting in reduced enzyme activity and the inability to metabolize acetaldehyde, a toxic byproduct of alcohol metabolism. This leads to a buildup of acetaldehyde in the body, causing unpleasant reactions like facial flushing, nausea, and rapid heartbeat after consuming alcohol [51]. Observant Mormons who routinely abstain from alcohol have the longest life spans among Americans, though this may also be due to other lifestyle factors in addition to sobriety [52].

Different pathogenicities of Epstein Barr Virus (EBV) in China and Africa: EBV is associated with multiple cancers. It causes oropharyngeal cancers in China and Burkitt's tumors in Africa [53,54]. This difference may or may not be genetic based as there are marked differences in culture, nutrition and prevalence of other pathogens in the two geographic regions. Racial differences in response to other infections, e.g., tuberculosis, and sepsis have been noted as well [55,56].

Gastric and Breast cancers: In addition to the differences in incidence of EBV induced tumors, other variations among different ethnic groups have been noted as well. The incidence of gastric cancer is higher, and the incidence of breast cancer is lower in Japanese as compared to Americans [57,58]. This difference is likely to be due to a combination of genes and culture as it tends to disappear over a few generations after immigration of the Japanese to the USA.

Differences in disease spectrum among Native Americans: The prevalence of obesity and diabetes are much higher in the Native American population than in white population. The differences are likely to be due to a combination of differences in genetic makeup and cultural practices. However, a logical explanation could be that the Native American population endured periods of starvation that favored the survival of people with more efficient metabolism. Those who could sustain themselves on a meager supply of food during food shortages, endured and survived the population bottlenecks [59]. Now that food is plentiful their efficient metabolism may be working to their disadvantage and resulting in obesity and diabetes [60].

Hypoglycemia induced by eating litchi/lychee fruit: A peculiar occurrence of hypoglycemia, occasionally fatal, in children, in India and Bangladesh, on consuming litchi/lychee fruit on empty stomach may be related to genetics and the background of undernutrition in affected children [61]. The occurrence of cirrhosis in children in India is similarly likely to be due to a combination of genetics and diet [62].

Cultural practices associated with health disorders: Cancer of the abdominal skin, "Kangri cancer" in Kashmiri people, in India, is almost certainly related to the practice of placing earthenware pots, containing live charcoal, under their clothing, on the abdomen, to ward against cold surroundings. The high incidence of oral cancer in Southern India may be due to the practice of reverse smoking, i.e., putting the lit end of the cigarette in the mouth. Beetle nut (Paan) chewing

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that contain tobacco is likely a contributing factor [63-65]. Some religious practices may be beneficial, e.g., Abstinence from alcohol among the observant Mormons and Muslims, avoidance of tobacco among the Sikhs, celibacy among observant catholic clergy and nuns. Consanguinity among some religious groups has negative effects on health [66].

Dietary practices and fads in different populations induce specific pathologies: The historical example of scurvy among sailors being a well-known entity. The current fascination with being "vegan" could produce nutritional deficiencies of vitamin B12, vitamin D, and other trace nutrients [67].

Ethnicity versus Precision Medicine: While it is desirable and noble to neutralize differences among different peoples, and avoid discrimination based on race, ethnicity, geographic origin or any other factors, this is in contrast to the principle of providing individualized, customized, precise care. The two competing philosophies need to coexist and ought to be balanced in healthcare including Laboratory Medicine [68].

Different results with different testing methods: Any given analyte may be tested by more than one method and the results from different methods may not be concordant. A few examples of this phenomenon are: (a) Measurement of blood hemoglobin by blood gas analyzer used in the emergency department gives a reading of one half to one gram higher than the analysis by the main laboratory method. (b) Whole blood glucose levels measured by point of care testing instruments are lower than the results of plasma glucose performed in the main laboratory. (c) Levels of troponin vary by more than 10-fold on different analyzers [69]. (d) Results by immunoassays are usually different from those by mass spectrometry. An international effort to standardize testing methods has succeeded in harmonizing measurement for only three analytes, namely, creatinine, hemoglobin A1c and Cholesterol [70]. Laboratories at different institutions may use different methods and a doctor with privileges at multiple hospitals would need to be conversant with the reference range/normal values at each site. While it is eminently logical that measurements for almost all, if not all, analytes ought to be harmonized, it is an intractable problem. Different parties develop assays for different analytes and commercialize their products. Even though the US Food and Drug Administration regulates body fluid testing, it does not demand harmonization. Just as approval for a new drug is granted if it is shown to be better than placebo, not better than exiting drugs, laboratory testing methods are approved without the need to show concordance with existing methods.

This lack of coordination of different testing methods is especially troublesome for tumor markers [71]. Almost all of the so-called tumor markers are used to monitor the course of disease, not for diagnosing malignancy. Given that different methods give different results, longitudinal monitoring of tumor markers to assess response to treatment requires that same laboratory be used for all tests. Change in the laboratory and or testing method requires re-baselining the results for longitudinal monitoring. Different troponin assays having a ten-fold difference in result values is not nearly as troublesome as a patient with myocardial infarction is usually an in-patient at one hospital and serial testing is done in the same laboratory with the same method.

Variation among Laboratorie

Different testing methods yield different results for a given analyte as addressed earlier [72]. In addition to the variation in results due to different methods, there is additional variation in results among laboratories using the same methods and instruments, including for analytes that have undergone international standardization, i.e., harmonization. To ensure accuracy of results, proficiency testing for regulated analytes is mandated by Centers for Medicare and Medicaid Services (CMS). Organizations authorized to conduct proficiency on behalf of CMS, called deemed entities, including College of American Pathologists, send samples to participating laboratories who test the specimens as they would test specimens from patients. The authorized entity analyzes the results from participants to ascertain if the performance of the laboratory is acceptable. The entity reports the lower and upper limits of acceptable results. One way to assess the variations among laboratories using similar methods is to assess allowed variation is the range of lower and upper acceptable limits for result from proficiency testing. Even for an analyte like creatinine, that has undergone harmonization, the difference in lower and upper limits of acceptable results is 35%. Similarly, the difference in acceptable lower and upper limits for TSH is also at about 35%, even when data involve results from laboratories using the same method and same instrument type. The much greater, 66% variation in lower and upper values for immunoglobulin G is a common level of variation in lower and upper acceptable limits. The degree/extent of variability in results among different laboratories may appear disconcerting, however, the variability on repeat testing in each laboratory is much narrower and argues for using the same laboratory for serial monitoring of a given analyte. Using the same laboratory for serial testing is especially important in monitoring tumor markers to assess response to treatment and course of disease.

Essential Nutrients

Laboratory testing for adequacy/sufficiency/optimal state for essential nutrients is complicated by the less-than-optimal standards. The recommended daily allowance (RDA) and by implication, the normal values, are geared to provide a value that prevents disease in 98% of individuals without health

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disorders [73,74]. RDA is meant to provide minimal levels to prevent disease and is not designed for optimum health. This conflict is well illustrated by Folic acid. The National Institutes of Health and Centers for Disease Control and Prevention (CDC) list normal level of serum folate/folic acid as >3.5 and >4.0 ng/mL. People with this level lack megaloblastic anemia in 98% of the instances. Some individuals with this level of serum folate have elevated serum levels of homocysteine and the values of this potentially injurious substance are normalized, in responsive individuals, if sufficient folic acid is administered to raise serum folic acid levels to >7.0 ng/mL. In January 1998, FDA mandated that folic acid be added to cereals as the supplement is known to prevent neural tube defects in the fetus. However, controlled trials showed the optimum serum folate level for maximum benefit is >13 0 ng/mL. A controlled trial in China demonstrated that Folic acid supplementation resulting in a serum folate level of >13.0 ng/mL reduced ischemic strokes in hypertensive patients [75,76]. These findings demonstrate that, there is a wide gap between the minimum essential level and the optimum level [73-77]. Evaluation of Vitamin D levels revealed a similar situation. Vitamin D serum level of 12.0 ng/mL prevents bone disease but a proportion of people with that level have elevated levels of parathyroid hormone. When supplemental vitamin D is administered to raise the serum levels to 20.0 ng/mL, parathyroid hormone levels get normalized. During most of human history, individuals were exposed to sun all day, and current populations with similar exposure have vitamin D levels of 50-80 ng/mL. It could thus be argued that normal serum levels of vitamin D should be pegged at 50-80 ng/mL [73,77]. Exposure to sun can provide sufficient Vitamin D for optimal health and sun exposure does not lead to vitamin D toxicity. While some foods are supplemented with vitamin D, about 80% of the US population has vitamin D levels lower than 30 ng/mL [78]. There is controversy about the benefits of supplemental vitamin D for preventing aches and pains, falls and fractures, hypertension, heart disease and general mortality rate. Vitamin D supplementation has been shown to have beneficial effects on the course of multiple sclerosis [79,80].

Contradiction Between Expert Opinions and Empirical Results

The generally cited reference value for serum albumin is 3.4 to 5.0 g/dL. However, data from life insurance companies reveal a higher mortality rate in people with serum albumin level <3.8 g/dL [81]. Examination of modifiable risk factors and mortality revealed that all-cause mortality is lower in individuals with non-HDL cholesterol of 200 mg/dL than in those with 100 mg/dL. Similarly, a person with a BMI of 30 has lower risk of death than one with a BMI of 20, despite the "desired" BMI being 18.5-25 [82]. Another paradox is the obesity paradox. Even though the risk of disease may be greater in obese individuals, the outcomes of acute illnesses, such as myocardial infarction, admission to intensive care unit and cerebrovascular accidents are better in overweight persons compared to normal weight individuals [83].

Cost of Laboratory Testing

While the cost of laboratory testing accounts for about 3% healthcare costs, in 2023 that amounted to about $150 billion/year in the USA. To put that in perspective, fewer than 67% of the countries have a GDP of $>150 billion. There are variable estimates of overuse of laboratory testing in the US with figures varying from 20-60% of the testing being unwarranted [84]. Some unnecessary testing is blamed on the need to practice defensive medicine. However, unwarranted testing begets more testing on the discovery of minor variations from the reference ranges. Paradoxically, recommendations of national and international expert bodies, e.g., International Myeloma Working Group, often end up promoting unjustified overuse of laboratory testing [85,86].

Comments

Clinical laboratory diagnostic testing is an integral and essential part of healthcare, however, the current state of the art in the accuracy and precision of results warrants caution in interpreting results and minor variations from normal ranges for diagnoses as well as monitoring of disease states. It is not my intent to shake your faith in laboratory test results but to encourage a more informed evaluation of the laboratory data. It is particularly important for a provider with privileges at multiple hospitals, and it is imperative that laboratory test results be viewed in the context of the home laboratory's reference ranges and similar caution needs to be exercised in patient transfers among institutions. Repeat testing for tumor markers in assessing the progress of patient should be obtained from the same laboratory to avoid the imprecision from using different methods and other variations in results from different laboratories. The same principle should be applied to other analytes that are often repeated over time and to monitor health and the results of treatment, e.g., TSH, blood lipids, CMP, immunoglobulins, etc. International standardization for the three analytes, namely, creatinine, cholesterol, and hemoglobin A1c, has not completely resolved the problem of variation in results from different laboratories. The range of upper and lower acceptable values may be disconcertingly large and variation on repeat testing could be addressed, in part, by using the same laboratory for serial testing.

It is recommended that Laboratory Medicine services, in addition to the reporting the reference ranges along with laboratory results, include a brief statement of the clinical significance of the results, especially for results for ambulatory patients. Clinically unimportant, minor variations in Mean Corpuscular Hemoglobin (MCH) Relative Width Distribution of red cells (RDW), pCO2, Sodium, Alkaline

phosphatase etc., could be annotated with a comment like, "No immediate concern". More meaningful results, e.g., a hemoglobin of less than 10 in males and 9 in females, fasting plasma glucose of 110-125, total serum proteins >9.0 and the like could have a cautionary comment like, "Discuss with your doctor at the next visit. Marked variations from normal results, e.g., hemoglobin <7.0, fasting plasma glucose of >130, serum creatinine >2.0 etc. could have a bolded comment like, "Contact your doctor at your earliest convenience" [22]. These statements would not replace the need for the laboratory to report critical/panic values to the healthcare provider. National organizations, such as the College of American Pathologist, and Association for Diagnostic Laboratory Medicine, could provide brief, uniform appendices that could be attached to the common laboratory test reports posted on the patient portals. In addition to the usual reporting and urgent reporting of critical values, a category of quasi-critical values has been proposed for results that warrant referral to a specialist but are not immediately life threatening. The common scenario of quasi-critical values is the first-time detection of a monoclonal immunoglobulin in specimens not ordered by a hematologist. In such circumstances, it is recommended that a secure message be sent to the ordering provider with a copy to the hematologists and hematopathologist to ensure that action on the finding is not delayed [87].

Conflict of Interest:

I serve as a consultant to Sebia Inc, Helena Laboratories, Diazyme Laboratories, Nexcella, Inc., Warm Springs GA Medical Center. I have applied for a patent for Serum free light chain antibody modified Serum immunofixation electrophoresis.

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