When is "abnormal" abnormal?

When is "abnormal" abnormal? Dealing with the slightly out of range laboratory result

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Results that lie outside the laboratory reference ranges are considered to be abnormal; however, various factors influence the tests. The users and patients must be informed of these limitations, so that laboratory tests remain a supporting piece of evidence in the clinical context and not a source of unnecessary concern.

The perception by users that results which lie outside our quoted reference ranges are "abnormal" and therefore require action results in additional testing and further investigation. It is also a source of worry for patients.

The use of population reference ranges is an inexact science that often does not consider age, sex, ethnicity and other influencing factors, and, in a setting of multiple testing, also does not consider the statistical likelihood of generating results that are out of range purely by chance. No simple answer exists of what should be done with the "slightly out-of-range" results, although providing better information for laboratories, users and patients will help in the most appropriate action (or inaction) being taken.

One of the questions occupying a large proportion of the primary care in pathology reviews in this journal¹ is the isolated "slightly abnormal" result in an otherwise fit person presenting with non-specific illness or as a result of "well-person" screening. This is a common cause of telephone calls, letters and referrals to secondary care and one that presents laboratory medicine and the user with a dilemma.

An abnormal result, however apparently clinically unimportant, is also a cause of concern for the patient and is potentially the origin of a cascade of further investigations. Although the answers in the primary care best practice reviews in this journal deal with specific test groups, some general trends emerge, which call for a pragmatic approach to the out-of-range result and for some basic information to be more readily available to the profession. This article considers slightly abnormal results in the non-acute primary care management setting.

WHAT CAN WE DO ABOUT THE CURRENT 95TH CENTILE REFERENCE RANGE?

A detailed discussion on reference ranges is beyond the scope of this article. Reference ranges of the 95 centile are quoted mainly for populations believed to be healthy, and occasionally for some analytes, are expressed as age or sex-adjusted ranges. As many analytes are not normally distributed and exhibit age, sex, racial and other demographic differences, and ranges depend on type of method, imprecision and bias, the reference interval is at best a loose approximation of what can be expected in an otherwise healthy population. On a purely scientific basis, it may seem attractive to try to express all reference ranges in their appropriate age, sex, racial and other relevant adjusted forms, although the ensuing chaos this may introduce among users makes this option seem impracticable, even if achievable. These difficulties make standardisation of existing ranges somewhat challenging.

Any answer to this dilemma will inevitably leave us with a situation in which 5% of values will lie (statistically) outside a 95th centile range and raise questions of further potential investigations in people without disease. It is tempting to move away from the conventional 95-centile range, whatever population it may refer to.

Many of us do not have ready access to information on the range of factors that influence population reference ranges for all of the analytes we measure, and it would be useful to have a readily available resource when faced with questions of results that are out of range.

SUGGESTION

We should have ready access to a robust database of factors that influence

reference ranges in specific populations for all of the common laboratory analytes in an electronic format, that is readily available to laboratory specialists, and where applicable, to users. Alternatives to the conventional 95th centile should be considered.

95TH OR 99.9TH CENTILE OF THE REFERENCE POPULATION

A recent paper² has proposed that laboratories move to a 99.9% reference interval to remove the number of false positives that occur with multiple testing, by using a 95% population reference range. With the 95% reference interval, only a few profiles (such as electrolytes, liver function tests and a full blood count) are required to result in around 20 analytes and therefore make it statistically likely that one of these will lie outside this interval. Statistically, probability thresholds for multiple test sets would normally apply the Bonferroni correction³ to take into account the number of tests used, and just one value outside the 95% limit would not usually be considered to be statistically significant when multiple tests were carried out. When associated with corroborative test results—for example, raised alkaline phosphatase and γ glutamyltransferase activities in a patient—the post-test probability of the result being clinically relevant clearly increases greatly.

Moving all reference ranges to a 99.9th centile population limit may remove false-positive results, but will increase false negatives and therefore shift the balance of risk of failing to diagnose clinical disease. This will be particularly true for those tests that exhibit low intra-individual variation compared with the interindividual population range, for which the change in individual value, even within a population range, is of greater importance than the value compared with the range itself.⁴

Such a movement also assumes that clinical significance correlates with the magnitude of the abnormality and this is clearly not always the case, as for example in chronic liver disease, where transaminase results may lie within or just outside the conventional 95% reference range.⁵ One risk in using this approach would be the generation of false reassurance in the face of a potentially relevant result, which may have attracted some attention outside the 95th centile but that is interpreted as entirely normal when it lies within the 99.9th centile range.

Several laboratories have adopted the simple and pragmatic approach of using an asterisk or other graphical system (example in fig 1) to display where a

result sits against a population reference range. Although this has undoubtedly been criticised for being unscientific, it does have the advantage of focusing a user's attention graphically on results that lie statistically further outside the reference range and are therefore potentially of greater clinical importance, without risking the possibility of a result that is slightly out of range being interpreted as clinically irrelevant. It perhaps comes closest to conveying the message that the slightly out of range result may be of relevance but is likely to be less so than a result many SDs from the mean.

SUGGESTION

Laboratories could use a graphical indicator to differentiate results that are just outside a reference range (eg, up to 3 SDs) from those that are statistically very unlikely to have been achieved by chance, and therefore unlikely to be false positives.

WHAT ACTION SHOULD WE RECOMMEND FOR SLIGHTLY ABNORMAL RESULTS?

Clearly, giving any generic recommendation that covers all situations is impossible. Despite the limitations of the population reference range, the proposal in Jorgensen's paper² may, however, be used as the basis to distinguish between the actions that may be considered for an out-of-range result. As a result outside of the 99.9th centile limit is not likely to have been obtained by chance; this would seem to be a reasonable level at which to recommend further investigation, unless the patient belongs to a subgroup that is known to have a different reference range (eg, a CK result of 300 IU/l in a person of Afro-Caribbean origin). As regression towards the mean⁶ results in many slightly out-of-range results returning to normal on retesting, it would appear reasonable in an asymptomatic patient to simply recommend interval retesting with further investigations only if the results are persistently abnormal over a

sustained period or if they become more abnormal.

SUGGESTION

In otherwise asymptomatic patients with no clinical indicators of disease, interval retesting should be considered in patients with results between the 95th and 99.9th centiles. Further investigation should be considered in patients with results outside the 99.9th centile limit. The time interval to retesting should take into account the possible disease process associated—for example, a retest interval of several weeks or even months in the event of slightly abnormal thyroid or liver tests.

WHAT ABOUT THE CLINICAL FILTER?

In an ideal world, tests are requested to answer a specific clinical question. In reality, however, profiles of tests are often requested in patients presenting with non-specific symptoms, in the hope of identifying a cause, and not infrequently identifying a non-specific abnormal test result instead. Where the pretest probability as indicated by clinical assessment is low, the post-test probability of an isolated result that is slightly out of range being clinically relevant is also low. The clinical filter should be applied before and after testing: in the case of abnormal liver enzymes—for example, focusing on the history of a patient with slightly abnormal transaminases—may show risk factors for non-alcoholic fatty liver disease that had not been apparent when the patient had presented. Any decision to further investigate or repeat the test after a prolonged period must also be based on the results of this clinical filter.

SUGGESTION

Improved guidance linking the utility of testing combined with clinical findings, particularly in non-specific situations, should be obtained and disseminated in suitable interventions (eg, electronic requesting filters) to limit indiscriminate testing in situations in which the pretest probability of disease is low (eg, multiprofile testing in non-specific illness).

CAN WE EMPOWER PATIENTS AND USERS BETTER?

The concerns or expectations of patients may often be a reason for tests being requested or repeated. Although it is entirely unreasonable to expect patients to be conversant with the statistical implications of a 95% reference range and population distributions that are not gaussian, most of my own patients

do seem to respond to the simple explanation that if we do a lot of tests on them it is not surprising that the occasional result will be slightly out of range and that this finding is probably only a statistical quirk. The more patients can be reassured that a slightly out-of-range result is in most cases unlikely to have any clinical relevance, the less our users are liable to feel obliged to investigate minimally abnormal results further. An excellent example of this can be seen in Lab Tests Online (UK).⁷

SUGGESTION

Further opportunities could be taken to inform patients and users about the limited clinical relevance of many one-off out-of-range results in otherwise fit patients and to abolish the myth that "out of range" is abnormal.

CONCLUSION

One danger of working in a laboratory discipline that relies on science to produce scientifically valid results is that we risk perceiving the discipline as being overly scientific. The final result of a laboratory test is ultimately the action taken by the requester faced with the result produced by the laboratory, which, in the case of the slightly abnormal result, is an extremely inexact science. We can improve information about factors that influence reference ranges, highlight results that are more likely to be clinically relevant than others, and inform users and patients about the limitations of normal ranges, but tests must ultimately remain a supporting piece of evidence in a clinical context. These interpretations should prove easier in the increasing number of situations in which clinical rules incorporate results into a set of clinical and laboratory findings used to assess pretest and post-test probabilities of disease being present from observational findings, and, in the ideal world, from evidence-based interventional studies.

A major factor in limiting the problem raised by slightly abnormal tests is to reduce indiscriminate testing in non-specific and unproven situations, where the pretest probability of disease is very low and where carrying out the test often only serves to increase the concerns of the patient and add unnecessary work for the practitioner.

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(A) Serum sodium 141 mmol/l [*]
(B) Serum sodium 132 mmol/l * []
(C) Serum sodium 125 mmol/l * []
(Reference range 135–145 mmol/l)

Figure 1 Simple graphical display of divergence of a result from a population reference range determined by results: (A) within range, (B) outside the 95th centile and (C) outside the 99.9th centile, as a visual prompt for users.

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