What is a “normal” test result? 
... a “normal” reference range?

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The word “normal” has many meanings:

ordinary, common, usual, standard, expected,

frequent, in agreement, natural, sane, desirable

... some special ones that don’t apply to tests:

Latin: norma, a rule

geometry: line or vector perpendicular to a plane or line;

chemistry: N, one gram-molecular weight dissolved in a liter,

or a straight-chain, aliphatic C-C-C hydrocarbon;

photography: a lens of moderate focal length;

education: school to train high-school graduates as teachers;

mathematics: real number with uniform distribution of digits, a type of function or measure in set theory, degree of a rational curve on a surface, and many others …

psychiatry: of sound mind, sane
... and some special ones that do apply:

**statistics**: the Gaussian continuous probability distribution, the “bell-shaped” curve; the study of groups, low emphasis on “outliers”

**medicine**: healthy, free of disease or loss of function, best possible state of being; focus on individuals, usually “outliers” different from most

**WHICH SHOULD WE USE for “normal”? Statistical or Medical?**

**CAN WE AGREE?** Get CONSENSUS?
Is It Healthy to be Normal?


This was a delightful and well reasoned commentary on an article published in that issue by Dutta, Saha, Johnson, and Chalasani, who had surveyed 67 Indiana laboratories where the upper limit of the “normal” range varied from 31 to 72. They concluded that different machines used to measure ALTs gave quite different results. In his commentary, Bob Dufour put his finger on a more likely explanation that people used to define limits were only “apparently healthy” and had other reasons for increased ALT values.

We shall be hearing from Bob Dufour very shortly.
--- this is not a new question, and dates back at least 10 years ---


*Using data from the Milan blood bank, they found that so-called “reference” populations used to set normal ranges included many people with NAFLD or unrecognized chronic hepatitis C. By excluding them, they found new, lower levels for “upper limit of normal” as **30 for men and 19 for women**, expressed as U/L, micromoles converted/minute/mL.*
Marshall Kaplan commented editorially in the same issue that consequences of this might overwhelm the health care system, make some people anxious, and decrease blood donors --- and dissented with what should be done with the findings of Prati et al.

**Alanine Aminotransferase Levels: What’s Normal?**

“I applaud Prati and colleagues for their carefully done study but would not adopt their recommendations.”
--- and so did I:

Healthy Ranges for Alanine Aminotransferase Levels.


TO THE EDITOR: …ALT assays are widely used as a screening test for detecting liver disease in apparently healthy people, in whom the prevalence of viremic chronic HCV infection is likely to be perhaps two orders of magnitude lower, or only about 0.6% (or 6 per 1,000).

Consequences of increasing sensitivity from 55% to 76% of patients with HCV antibodies was attended by a decrease in specificity from 97.1% to 88.1% and great decrease in the value of a positive test result, from 11.9% to 4.0%, which means that a positive result of the new test would be WRONG in 96%, due to the increased numbers of false-positive results.

They replied that they did not propose the changes for screening, but to follow and monitor HCV-positive patients over time, and believe that ALT values are best used flexibly as a continuous, not dichotomous, variable.
I cannot conceal my bias in favor of considering that the desired range of *normal* should be derived from healthy, well people, rather than a statistically common or frequent group of people that may include sick or abnormal people who may not even know it.
Are subjects selected for controlled clinical trials all healthy, normal? Not necessarily, as we shall consider this afternoon when discussing the flood of new drugs and combinations coming to treat or possibly “cure” chronic hepatitis C.

Many or most of them will not have normal healthy livers before starting treatment, so should they be compared to healthy, normal people … or maybe not, but alternatively to *themselves in how they respond to treatment*. Maybe we should figure out how to do this.
Let’s think a little about how we might find a “baseline” in some way better than the usual assumption of a single pre-treatment point, knowing that a single point does not define a line, and we shouldn’t just assume it is horizontal, indicating that it’s how it was and would be if no intervention occurred…

*(you can insert new dates and values in the little program on the next slide and see what happens…)*
Calculate BASELINE from screening & pretreatment values

...an Excel program,-bslncalc.xls

Take ALT as example, tests 3 weeks apart:
Use both screening and pre-treatment test results.

*(do not start treatment until results of pre-treatment test known)*
*(If slope of ALT values rise at >30% per month, best not to start experimental drug or controlled study, but investigate for probable cause of rising values.)*

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<tr>
<th>screening date</th>
<th>value, U/L</th>
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<tbody>
<tr>
<td>29-Jan-13</td>
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<table>
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<tbody>
<tr>
<td>17-Feb-13</td>
<td>36</td>
</tr>
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</table>

slope: 0.200  PROCEED

baseline: 34  average of 2
You’ll be hearing more shortly from Dr. Leonard Seeff about why it’s a good idea to calculate a baseline slope using both screening and immediate pretreatment test values … rather than using the conventional “upper limit of the normal range (ULN)” in groups of healthy, normal people for comparisons of effects.
But now, let’s hear from Bob Dufour about what really is, or should be, considered “normal,” and let the debate commence…