Well, over the past several years in preparation for these meetings, my good friend John Senior would come to me and say, would I please give a talk on the role of the ALT as a quote "biomarker" for drug-induced liver injury. And like a good soldier, I respected the invitation and say, yes, I would do so.

And I have done this several times. Each time it has been exactly the same as it had been the year before. So, it has been a very boring presentation. So, he came to me this time and said, "Well, you must have learned something. Maybe you're going to make a better job of it this time." And I regret to say that what you will hear is exactly what I have been saying for the last several meetings. So, please sit back and be prepared to be bored by all of this. (Laughter.)
As we know, at the present time there is no definitive biomarker for drug-induced liver injury (DILI). The whole issue, then, of causality assessment for DILI is an inexact science.

We are still dependent on serum enzymes, particularly ALT, but also the AST and alkaline phosphatase, as a trigger of interest. It is not a diagnosis of drug-induced liver injury, but it is a trigger to tell us that there is some liver injury.

And so, the problem we have is: what are the levels of ALT abnormality that we should consider to be of importance? There are a number of shortcomings, as you know, with respect to the ALT as a, in quotes, "biomarker". I list four here.
The first is that it is a non-specific marker of liver injury and not of drug-induced liver injury. It requires, then, as we have heard, that all other causes of liver injury first be excluded before you can consider the possibility of incident drug-induced liver injury.

Second of all, there is no consensus on what level of ALT increase during treatment should signal possible incipient drug-induced liver injury. Should it be three times? Should it be five times? Should it be eight times?

Thirdly, as we have heard this morning, whatever the agreed-upon ALT level, it has to be measured against a background, a comparator, and the comparator is usually the baseline level. The baseline level that people consider to be important is what we call the, in quotes "upper limit of normal." As we have heard today, there is a lot of dispute on what the upper limit of normal is.
Finally, there is a whole new paradigm, and that is, now that we have the very potent antiviral drugs for hepatitis C, we are bringing into the fold people who already have abnormal enzymes to be treated. And so, how do we then use that same abnormal enzyme as a biomarker, as a marker of potential DILI? So, these are the four issues that seem to be we have to consider in the whole issue of the ALT as a biomarker.
It is also complicated by the fact that there is a complete difference between assessing drug-induced liver injury in clinical trials as compared to assessing it in clinical practice. In clinical trials, mostly people who come in, the choice generally, other than people who have been treated for chronic liver disease, is to bring in people who start with normal enzymes, below whatever level is considered to be the upper limit of normal.

Second of all, these individuals are generally monitored for the possible development of drug-induced liver injury. So that, if we begin to, then, consider what components we have to take into account in trying to assess, look at causality assessment of drug-induced liver injury, we have the components.

In clinical practice, on the other hand, we learn about drug-induced liver injury when a patient has been on a particular drug for a while. They develop symptoms. There has to be something that causes concern to the clinician. They either have symptoms or they have jaundice, and they are on a drug. You think to yourself, well, maybe this is drug-induced liver injury.

And so, in this case we do not have a baseline. We do not have preexisting serum enzymes in which to make comparison. So, the role of the ALT, then, is somewhat different in this setting than it is in the situation of a clinical trial.

So, I would like to go through each of these four areas, as I have just mentioned. Let me start off with the impact of the ALT as a nonspecific diagnostic marker.

The diagnosis or the consideration, not the diagnosis, the consideration of potential DILI is a circuitous event. We cannot, on the basis of an abnormal ALT, call this drug-induced liver injury. We have to go through the whole process of screening, as Naga mentioned earlier, for the hepatitis viruses, including hepatitis E that people sometimes forget, for autoimmune hepatitis, for alcohol, et cetera, et cetera, or fatty liver disease.

The result of this is that it is a very protracted assessment that has to take place, which is costly. If we had a specific test that would tell us this is drug-induced liver injury, we wouldn’t have to pay for all these tests. So, the downside of having a test which identifies liver disease, but not specifically drug-induced liver injury is cost. At least one part of it is cost.

The other part of it, of course, is that there may be a drug that is withdrawn prematurely while the patient is being evaluated for the possibility that the problem is, in fact, drug-induced liver injury. This may have a negative effect. So, you know, it would be, then, ideal or much better for us to be able to have a very specific test that says this is drug-induced liver injury, which the ALT is not.
Secondly, we come to this issue of what should the level of abnormal ALT be that signals possible impending DILI. Let me again reemphasis and I guess Arie has made this point and I think Naga as well that finding that normal ALT does not diagnose drug-induced liver injury. It tells you that there is some abnormality, and the important thing to do is to go through the whole process of causality assessment, which largely requires you to exclude all other causes before you come down to the possibility that this is drug-induced liver injury.

Most trials have required bi-weekly or monthly ALT monitoring to screen for possible developing DILI, which gives us the components in which to assess identification of abnormal levels. But the question is, what should that level be that leads you to worry about the possibility of drug-induced liver injury?
It is my view and maybe the experts in the field here are going to tell me it is quite wrong that, in general, ALT levels that are in the normal range, whatever that happens to be, remain pretty normal over time in persons who don't have liver disease. So, therefore, I suggest that as little as a twofold increase of the ALT in people who are monitored with prior normal values can at least raise concern for impending DILI in the appropriate setting. That is people who are taking drugs and within six to nine months this abnormality happens.

However, obviously, this level of ALT increase is rarely accepted as a reason to withhold a drug, unless accompanied by symptoms or jaundice, although it should trigger repeat ALT testing. However, higher levels as signals for possible developing DILI have been suggested, but each are simply arbitrary choices.

So, therefore, higher levels of signals for possible DILI have been suggested, but I must state that, in my view, whatever level of cutoff, it is all arbitrary. We don't really have a number that really tells us that this is more meaningful. As we heard, is it 265 or 275? Whatever the choice is, it is somewhat arbitrary, but we need something to hang our hats on. So, what are the levels that have been suggested? Well, as we have heard, it is either a threefold increase or a fivefold increase or maybe even an eight-to tenfold increase.
There is a recent effort to look at this issue, and in an important paper it was suggested that a fivefold increase should be the level that leads you to be concerned. The reason given for that is that you don't want to bring in people who have underlying chronic liver disease that is not easily recognizable, such as fatty liver disease or maybe chronic hepatitis C.

I believe that certainly in the setting of the clinical trials this is not an issue because you bring people in. By and large, you have normal values and you have sequential values that you test and they are normal. People with fatty liver disease are not going to suddenly develop an abnormality. So, I think that fivefold is too high a level, and I believe that a threefold increase should be a more practical and appropriate signal for possible impending DILI, not a diagnosis of DILI, but to consider the possibility that this may be a problem that needs further evaluation.
Well, given the fact that there is a threefold or fivefold, it is against what? What is the comparator baseline level? Well, as we have heard, normally, the traditional baseline comparator is regarded as the upper limit of normal, but this is determined for each lab, as we heard, by screening large local populations believed to be healthy and, then, selecting as a reference number the mean value plus or minus two standard deviations (95th percentile).

Unfortunately the screened local population is not always healthy, some having unrecognized NASH causing raised ALT levels, thus increasing the mean level of the ALT.
If you have clinical trials and several research labs participate in this trial, it is likely there will be differing levels identified as the upper limit of normal. This will, obviously, have an impact on defining the fold increase level used to signal impending dil.

To avoid this problem, the baseline comparator used to establish a given ALT fold increase would have to be the ULN value established by each laboratory separately and not a hypothetical group normal value.

A preferable alternative is to use each individual's own baseline ALT value as the comparator.

So, I think to avoid this problem, the baseline comparator used to establish a given ALT fold increase would have to be the upper limit of normal established by each laboratory separately, if there are several labs involved, and not a hypothetical group normal value. A preferable alternative, in my view and I have suggested this before, and I don't think that it has taken off is that, ideally, I think it will be better to have each individual's own baseline level as the comparator. So, you would, then, start out with a person, have their level, and any subsequent increase of three times is made on the basis of their own baseline level that they started with.
Now let’s get to this issue of DILI monitoring guidelines for persons with preexisting abnormal ALT levels. As you know, with the advent of these wonderful, new drugs, the majority of people who have been treated for chronic hepatitis C respond dramatically. Over 90 percent lose their virus and enzymes soon come down.

Remember that chronic hepatitis C is the focus of attention at the moment, but in the future there may be other forms of chronic liver disease, such as fatty liver disease, NASH, NAFLD, and so on, that will be subjected to treatment trials starting with abnormal ALT levels.

For these individuals with already raised ALT levels at the outset, the use of ALT as a signal for a possible DILI is a problem. Of course, the FDA guidelines, as you know, did not establish any rules for persons who enter trials with abnormal ALT levels to begin with.
So, as I mentioned, the DAAs are highly effective. What happens, within a couple of weeks, the serum enzymes come down to normal; the virus disappears, but they continue to be treated for approximately 12 weeks, although that may change in the future. During that time, the values may go up again. And then, you have to worry, could this, in fact, be potential DILI? So, this raises the question of what the comparator should be if an elevated ALT develops thereafter - the original baseline abnormal ALT level, or the new on-treatment normal ALT level?

So, for those people who are responders to the DAAs, the Direct-Acting Antivirals, the majority of them return to normal on treatment, and if followed by a rise in the ALT levels, assessment for possible DILI can no longer be measured against their baseline level since the ALT levels may have declined because of treatment. A subsequent increase should, therefore, be compared with a new on-treatment level of ALT if the concern being raised is the increase exceeds two- to threefold. Obviously, reappearance of HCV-RNA would suggest, in fact, that there has been a viral breakthrough and not drug-induced liver injury.
What about the very few people who have been treated and coming with chronic hepatitis C, are being treated and don't respond? This is relatively uncommon. I would suggest that they should be measured against, again, their own baseline abnormal ALT level, not some hypothetical group normal.

The following approach is suggested: if the abnormal baseline ALT value does not exceed 100 U/L, a 3-fold ALT increase over the baseline would represent an increase of concern; if the baseline ALT is abnormal but exceeded 100 U/L, a 2-fold ALT increase over the baseline would be an increase of concern.
If the baseline level is abnormal, but exceeds 100, I would get concerned if the ALT increase doubles and I wouldn't wait for it to be triple before I would get a little bit concerned about that.
And what clinical practice? Well, as I have mentioned, we don't have all the baseline information in clinical practice that would permit us, in fact, to look at an ALT compared to baseline, because we don't have a baseline. This is a different beast altogether, and this is the whole area of causality assessment that a number of people, some well-known people in this audience have been studying all the time.
And causality assessment, then, rarely I think is not based on the level of ALT. In fact, the ALT simply confirms there is liver disease. These are patients who come in who are being studied because they feel lousy, they've got fatigue, they've got muscle pain, blah, blah, blah. They're jaundiced. You do serum enzyme testing and they have an abnormal ALT, and it doesn't matter what the level is, at this point you, then, go through the causality assessment that I guess we are going to hear from Naga at the moment and that DILIN is doing and the other well-known groups in this audience are involved in doing.
So, this is exactly what I was trying to say. I am going to conclude with the following: the lack of a definitive biomarker for DILI places the burden on screening for possible emerging DILI on the ALT value. There is presently limited consensus on how best to apply the ALT for this purpose. Greater consistency in setting the parameters of its applicability is needed until it is replaced by better means of detecting incipient DILI. And this is where all the wonderful efforts that are being undertaken at the moment to identify more specific biomarkers becomes extremely important. And just to remind you that the approach to screening for DILI differs depending on whether it occurs during a clinical trial or in clinical practice. Thank you very much.