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Clinical Application of High-Sensitivity Cardiac Troponin Testing in the Emergency Setting

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Webinar Transcript with Mandarin Translation

Speaker

Peter Kavsak PhD, FCACB, FAACC, FCCS

Professor and Clinical Chemist

Department of Pathology and Molecular Medicine, McMaster University and Juravinski Hospital and Cancer Centre, Hamilton Health Sciences, ON, Canada

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Good afternoon and welcome to today's webinar, Clinical Application of High-Sensitivity Cardiac Troponin Testing in the Emergency Setting. My name is Joyce. I work in the education team at AACC and I'll be your moderator. We are delighted to bring you this webinar, presented by AACC and generously supported by Beckman Coulter China. This program is accredited for one excellent continuing education credit. I'd like to point out that this Webinar and the following question and answer session has been recorded in advance and can be stopped and started at any time. For viewers who would like a transcript of the audio of this presentation in Mandarin Chinese, please note the link to this resource is provided directly beneath the Webinar viewing window. So let's get started. Thank you for joining us today for today's Webinar, Clinical Application of High-Sensitivity Cardiac Troponin Testing in the Emergency Setting. Please welcome our presenter Dr. Peter Kavsak, a Professor in the Department of Pathology and Molecular Medicine at McMaster University in Hamilton, Ontario, Canada. He is also a Fellow of the Canadian Academy of Clinical Biochemistry, and the AACC Academy, the academy of American Association for Clinical Chemistry, and the Canadian Cardiovascular Society. He provides service as a clinical chemist within the Hamilton Regional Laboratory Medicine Program and is primarily based at the Juravinski Hospital and Cancer Centre with special clinical and academic focus and interests in the cardiac and cancer related laboratory tests. Previously, he was Editor-in-Chief for Clinical Biochemistry and he is an Editorial Board member on 5 different scientific journals, most notably Clinical Chemistry, and Clinical Chemistry and Laboratory Medicine. He has over 180 publications, with approximately 70% in the cardiac field. He is also currently a 2nd-term member on the IFCC Committee on Clinical Applications of Cardiac Bio-Markers. Dr Kavsak, we're glad to have you present today, you may now begin your presentation.

下午好，欢迎参加今天的网络研讨会，高灵敏度心肌肌钙蛋白检测在紧急情况下的临床应用。我叫乔伊斯。我在 AACC 的教育团队工作，我将担任你们的主持人。我们很高兴为你们带来这次由 AACC 主办，由贝克曼库尔特中国慷慨支持的网络研讨会。这一项目有继续教育一个学分的认证。我想指出的是，该网络研讨会及随后的问答环节已预先进行了录制，可以随时停止和开始。对于希望获得此中文普通话音频的文本记录的观众，请注意，该资源的链接直接提供在网络研讨会观看窗口下方。好的，让我们开始吧。感谢加入我们今天的网络研讨会，高灵敏度心肌肌钙蛋白检测在紧急情况下的临床应用。有请我们的讲者，彼得 卡夫萨克（Kavsak）博士，他是加拿大安大略省汉密尔顿麦克马斯特大学病理学和分子医学系的教授。他还是加拿大临床生物化学学院、美国临床化学协会（AACC）学院和加拿大心血管学会的会员。他在汉密尔顿地区检验医学项目内提供临床化学家的服务，主要是在 Juravinski 医院和癌症中心工作，临床及学术领域主要关注及兴趣在于心脏及癌症相关的实验室检测。此前，他是《临床生物化学》的主编，目前是 5 本不同科学期刊的编委会成员，其中最为著名的是《临床化学》以及《临床化学和检验医学》杂志。 他有超过 180 项发表，其中约 70％在心脏领域。他目前是 IFCC 心脏生物标志物临床应用委员会的第二届成员。卡夫萨克博士，我们很高兴今天您能来到这里，您现在可以开始演讲了。

Well, thank you very much. First of all, I'd like thank Beckman Coulter and Beckman Coulter China for the opportunity to speak to you today about high-sensitivity and AACC's support for facilitating these educational events. So we'll get started.

好的，非常感谢。首先，我要感谢贝克曼库尔特和贝克曼库尔特中国，今天有机会与你们谈谈高灵敏度，也感谢 AACC 为促进这些教育活动提供的支持。好的，我们开始吧。

So I've choosed this title of this talk, clinical application of high-sensitivity cardiac troponin in the emergency setting. And let me just say that this has been the focus of mine for past dozens years. So it really is a pleasure to talk to you about some of the stuff we've done in the past as well as other work and other advance in the field because the area has tremendously evolved in the past dozen years regards cardiac troponin measurements and specifically in regards to high-sensitivity troponin.

我选了本次演讲的题目，即高灵敏度心肌肌钙蛋白检测在紧急情况下的临床应用。我只想说，这是过去几十年来我一直关注的重点。很高兴与你们谈谈我们过去所做的一些工作以及该领域的其他工作和其他进展，因为在过去的十年中，该领域在心肌肌钙蛋白检测方面取得了长足的发展，特别是关于高敏肌钙蛋白。

So the first thing I want to notice is I do have disclosures from industry, that are listed here. I'm also very grateful for industry supports that allowed me to perform various studies over the number of years. As well not listed on the disclosures, I'm very thankful as well for the public support that I received from granting agencies that has also suported some works that I'll be presenting.

我要讲的第一件事是，我确实有来自行业的披露，在此列出。我也非常感谢业界的支持，这些支持使我多年来可以进行各种研究。还有未在此披露的，我也很感谢我从资助机构获得的公众支持，这些机构也支持了我将要展示的一些内容。

So the objectives for today's Webinar are as follows: the first one is to discuss the analytical attributes of a high-sensitivity cardiac troponin assay. The second is to plan quality control testing specific for high-sensitivity cardiac troponin testing. And the second one is really something that in laboratories we should be doing. And I'll present some data on how laboratories can improve service in this regard. And the third objective is to kind of review and evaluate the strengths and weaknesses for earlier testing protocols for high-sensitivity cardiac troponin in the emergency setting. And this has gained a lot of attention obviously on the laboratory side, perhaps more importantly on the clinical side, when evaluating patients' fluids with potential chest pain.

今天的网络研讨会的目标如下：第一个是讨论高灵敏度心肌肌钙蛋白检测的分析特性。第二个是针对高灵敏度心肌肌钙蛋白检测的质控测试做出计划。第二个确实是我们应该在实验室中做的事情。我将提供一些有关实验室如何在这方

面改善服务的数据。第三个目标是回顾和评估在紧急情况下高灵敏度心肌肌钙蛋白检测早期检测方案的优缺点。在评估潜在胸痛患者的体液时，这显然在实验室方面引起了很多关注，也许在临床方面更为重要。

Okay, so where do we begin. The first thing is that I really recommend everyone to look at the following publication that published in April and issued of 2018. It was a joint effort by the AACC academy and the IFCC committee on cardiac biomarkers, where we provided ten recommendations on laboratory testing. It's specifically with a focus on high-sensitivity troponin. So of the ten recommendations, I just want to focus, perhaps narrow it down to a few of them that are relevant pertinent for this presentation. The first is, the fourth recommendation is actually on the 99th-percentile, you cannot give a talk with cardiac troponin without obviously highlighting the 99th-percentile. And there will be some discussion on there. And the fifth recommendation from this guideline or this paper is on the classification of cardiac troponin assay. So these will be equally, these two recommendations are really going to be the focus for objective one. The first recommendation that was in this document is actually on quality control practices and specifically with a focus on high-sensitivity troponin. Obviously the second and the third follow up on that. And that's really gonna be the focus on objective two. And finally objective three, I think it's important that the laboratory to understand some analytical variables that can impact on clinical interpretation, I've highlighted in their recommendation #7. And finally the last recommendation talks about what's actually a change when we think about troponin values of series measurements. And again that will also be discussed.

好的，那么我们从哪里开始呢。首先，我真的建议每个人都看看下面这篇 4 月发布并于 2018 年发行的出版物。这是 AACC 学院和 IFCC 心脏生物标志物委员会的共同努力，我们在实验室检测方面提供了十项建议。特别关注是高敏肌钙蛋白。在这十项建议中，我只想关注，或将范围缩小到与本次演讲相关的一些建议。首先是，第四项建议实际上是关于 99 百分位数，如果重点强调 99 百分位数，是没办法讲心脏肌钙蛋白的。关于这一点将会有一些讨论。本指南或本文的第五条建议是关于心肌肌钙蛋白测定的分类。这些是等同的，这两项建议实际上是目标一的重点。该文档中的第一个建议实际上是关于质量控制实践的，尤其是针对高敏肌钙蛋白的。显然，第二和第三个是后续跟进。这实际上是目标二的重点。最后是目标三，我认为实验室了解一些可能影响临床解读的分析变量很重要的，我在建议 7 中强调了这一点。最终，最后一条建议讨论了当我们考虑系列测量的肌钙蛋白值时实际上发生了什么变化。这一点同样将会讨论。

So as mentioned this has been a twelve year plus journey for me. Specifically with Beckman Coulter, we published the first analytical characteristics and utility of a high-sensitivity cardiac troponin assay in Clinical Chemistry back in 2009. And so what was very interesting in 2009 is that we actually measured samples in 2007 and samples were collected in mid-90s. And we measured it with the prototype assay. That was in 2007. We kept those samples and we measured those same samples twenty years later, so with regulatory-approved Backman Coulter assay. So as you can see on the right side of the slide you can see the bottom, you will see a Beckman's 2007, that's the prototype assay. That was a research assay. Versus on the y axis the

Beckman 2007 high-sensitivity troponin, the regulatory approved assay. And so what's really remarkable here is that on samples have been collected over twenty years measurements by two different assays ten years apart, we can actually see remarkable agreement between the concentrations. Now you know the regression sustained with the slop now a little bit different and so forth. But I really want to stress the fact that if an assay is designed appropriately, you will be able to monitor and pick up cardiac troponin and examples sort of for quite a number of years. So this goes with stability of analyte. But importantly it has to go with the assay's stability to monitor that. The last thing I want to highlight the fact that, this's gonna be the topic for later as well, as you can see with the prototype Beckman assay, the research assay in 2007, we had a couple of these huge outliers which have obviously in the 2007, for approved assay that they are actually at a lot lower concentrations. So I just want to plant that seed in your mind as when we think about factors perhaps affect troponin measurements, why are there differences sometimes between assays. And you'll be able to see, in the subsequent slides, that improvements over the past dozen or so years effectively led to reductions of some of these analytical aspects. And perhaps elevations.

因此，如上所述，对我来说已经十二年多了。特别是与贝克曼库尔特一起，我们早在 2009 年就在《临床化学》上发表了高灵敏度心肌肌钙蛋白测定法的首个分析特征和用途。因此，2009 年非常有趣的是，我们在 2007 年实际测量了样本，而那些样本是在 90 年代中期收集的。我们用的原型测定对其进行了测量。那是在 2007 年。我们保留了这些样品，并在 20 年后对这些样品进行了测量，用的是监管机构批准的贝克曼库尔特检测。你们可以在幻灯片的右下方看到，可以看到贝克曼 2007，就是原型检测。那是个研究的分析。与之相对的 y 轴是贝克曼 2007 高敏肌钙蛋白，监管机构批准的分析方法。而这里真正引人注目的是，对二十年前采集的样品进行两次相隔十年的分析，实际上可以看到浓度之间显著的一致性。现在你们知道由斜率的回归现在有少许不同。但我想强调一个事实，就是如果检测方法设计合理，你们可以在相当多年的时间里监测并测初心肌肌钙蛋白及其样品。所以这与分析物的稳定性有关。但重要的是，检测要稳定才能对其进行监控。我想强调的最后一点事实是，这也是之后要讨论的话题，你们可以看到用贝克曼分析原型，2007 年的研究分析，我们有几个明显的离群值，在 2007 年对于批准的分析，它们实际上的浓度很低。因此，我只想在你们脑海里种下那颗种子，当我们考虑可能影响肌钙蛋白测量的因素时，为什么有时分析之间会有差异。在随后的幻灯片中，你们将看到过去十几年来的改进有效地使得这些分析方面有所减低。也许还有升高。

Okay, so the analytical attributes of high-sensitivity cardiac troponin assay, so there are two main aspects of this. First, the %CV at the 99th percentile should be ten percent or lower and obviously that is an important metric when we talk about precision. And the second is that measurable concentrations should be attainable at a concentration at or above the assay's are limit of detection for greater than fifty percent of healthy individuals. So these two criteria are something laboratory can provide, obviously should be able to monitor assay to appropriate position and importantly, obviously if you have the resources you will be able to perform a reference interval study to demonstrate that indeed a majority of the patients or healthy individuals are both fifty percent above the LoD.

好的，高敏心肌肌钙蛋白测定的分析特性，有两个主要方面。首先，99 百分位数的%CV 应该为百分之十或更低，这显然是在我们讨论精度时的一个重要指标。第二点是对于超过百分之五十的健康个体，可测浓度应达到或超过检测限度的浓度。因此这两个标准是实验室可以提供的，显然应该能够将检测监测到合适的位置。并且重要的是，显然，如果你们有足够的资源，你们就能够进行参考区间研究以证明确实大多数患者或健康个体都比 LoD 高出百分之五十。

So how was it, how is it to monitor a contemporary assay at 99th percentile. So prior to a switching from contemporary assay to a high-sensitivity assay, we actually manufactured and made a material, quality control material, near of the 99th percentile, which for this assay was point o three. And so you can see that this is our quality control material measurements over two years and you can see that the type of precision here with contemporary assay. It's very challenging to meet the criteria. I mean this type of variation that you see here, the shift up, the failures. What have you, on regarding quality control. This represents a 20%CV at 99th percentile concentration with a contemporary assay. So this is actually still a guideline compliant when you think about contemporary troponin assays that they allow a CV at 20% at 99th percentile. But you can see as well that how challenging this was for us to monitor and provide, as best as we could, reproducible results at 99th percentile. So this is a contemporary assay. What happens when we switch to a high sensitivity assay?

因此，它如何在 99 百分位数对一个传统分析进行监测。其实在从传统分析转换为高敏分析之前，我们实际上制造并生产了一种材料，质量控制材料，接近 99 百分位数，其对此分析而言是 0.03。因此你们可以看到这是我们两年来质控材料的测量结果，并且可以看到采用传统分析方法时的精度类型。打到标准是非常具有挑战性的。我的意思是你们在这里看到的这种变异类型，上移，失效。至于质量控制。用传统分析法，这表示在 99 百分位数时的 CV 为 20%。因此当你考虑传统肌钙蛋白测定时，它们允许 CV 在 99 百分位数时达到 20%，实际上这还是符合指南的。但是你也可以看到，这对于我们，尽力而为的情况下，在 99 百分位数进行监控并提供可重现结果是多么具有挑战性。所以这是一种传统方法。当我们转为高灵敏度检测时会发生什么？

We can see here with a high-sensitivity assay the concentration that is well below the limit of detection, so this is 4 ng/L or would equivalent be 0.004. And again, most contemporary assays can measure below 0.01 ng/mL, 0.01 μg/L. So this represents quality control material that would be undetectable of contemporary assay. Of the high-sensitivity assay, not only can we detect these concentrations, but we can achieve precisions that are around four with fantastic or reproducability, fantastic precision less than fifteen percent, a value that would be well below the 99th percentile. So just by objective metrics how well we can measure normal concentration, high-sensitivity greatly exceeds performances compared to contemporary assay. And this type of performance is also applicable and evident when looking at the 99th percentile.

我们在这里可以看到用高灵敏度检测，浓度远低于检测限，浓度是 4 ng/L 或等效为 0.004。同样，大多数传统测定法可以测量低于 0.01 ng/mL，0.01μg/L。所

以这意味着传统检测无法检测到的质控材料。在高灵敏度分析中，我们不仅可以检测到这些浓度，而且可以达到极佳的或可重复的精度，达到大约 4 的精度，极高的精度不到 15％，该值将远远低于 99 百分位数。所以仅凭客观指标，我们能多好地测量正常浓度，与传统测定法相比，高敏在性能方面大大超越。当看 99 百分位数时，此类性能也适用并很明显。

So here we can see using, again, a quality control material near, this is patient pool material, near the male 99th percentile. We can actually see that if we look at here, the distribution of all the results. Again this is approximately a year results closed to two thousand data points. Each of the curves that goes into the distribution curves are are different analyzers. And what we see here is the fact that there is really no difference between the sites. We are able to demonstrate appropriate precision at 99th percentile and really there is no difference between the analyzers at the different sites. So this goes the fact is that having a high-sensitivity you're able to achieve precision below the 99th percentile and more importantly you actually are able to demonstrate very close agreement between the different sites as well. So this would mitigate and help prevent this classification of patients presented one hospital versus another to do this as superior performance.

所以在这里我们可以再次看到，指控材料接近，这是患者库材料，接近男性 99 百分位数。实际上我们在这里可以看到，所有结果的分布。同样，这是大约一年的结果，接近 2000 个数据点。分布曲线中的每条曲线都是不同的分析仪。我们在这里看到的是两个站点之间确实没有差别。我们能够在 99 百分位数显示出合适的精度，并且在不同地点的分析仪之间确实没有区别。因此，事实是用高敏，你可以在 99 百分位数以下实现精度，更重要的是，你实际上还可以证明不同站点之间的紧密一致性。因此，这将减少并有助于防止某家医院对另一家医院的此类患者出现性能优效。

So one other thing, obviously the fact is we have better precision with the high-sensitivity assay. But the other aspect is measurable concentrations. And so one way to think about this is the typical iceberg. With a contemporary assay where we couldn’t measure really normal individuals. What we focused on was the fact that how well we could measure at 99th percentile. And this is where we try to achieve a 10%CV and we can allow up to 20% and that was demonstrated earlier. As we should you, it was very challenging to do that. But that's where we are at the current contemporary assays. We are just focus on how well can we measure at the 99th percentile. With high-sensitivity assay, not only can you measure very well with the 99th percentile very precisely, more importantly we're able actually to detect troponin in the vast majority of individuals. And this type of information obviously coupled to how well we can measure troponin precisely. The fact that we can actually detect normal concentrations is really important when we think about earlier diagnostic algorithms and change criteria and able to re-stratify. This can only be done with high-sensitivity assay. And so, below here at the slide you can see two publications from 2009, one in New England Journal Medicine, one in Clinical Chemistry. And the one on New England Journal Medicine very important publication by Keller et al. from Stefenblankenburg's group, looked at Siemens Ultra assay. It is not a high-

sensitivity assay. It is a verry good assay, but it is not a high-sensitivity assay. This Siemens Ultra assay. Siemens does also have now a high-sensitivity assay. But at the time of 2009, this was a contemporary assay. So you can see here, here's a 99th percentile. Realistically you know close to four thousand individuals they measured. Vast majority of these individuals had undetectable concentrations. Now how dose this compare to a high-sensitivity assay? Now here is the prototype version that we worked with Beckman Coulter. And now you can see that there are limited detection somewhere around here. We can actually see that there is a nice kind of distribution. We're able to measure troponin in the vast majority of individuals. And it's not quite Gaussy in you know normal distribution. But we are somewhere getting a close to normal distribution, or at least measurable concentrations. So this is again a very unique attibute of high-sensitivities and we'll be able to measue troponin in vast majority of individuals.

所以另一件事，显然是事实是，我们通过高敏测定获得了更高的精度。但是另一方面是可测量的浓度。因此，考虑这种情况的一种方式就是典型的冰山。用传统分析方法，我们无法测量真正的正常个体。我们关注的事实是，我们在 99 百分位数上的测量能有多好。这就是我们试图达到 10％CV 的地方，我们最多可以允许 20％，这在之前已经说明。正如我们应该的那样，做到这一点非常具有挑战性。但这就是我们目前传统分析的水平。我们只是关注于在 99 百分位数上的测量有多好。有了高敏分析，你不仅可以非常精确地在 99 百分位数测量地非常好，更重要的是，我们实际上能够在绝大多数个体中检测肌钙蛋白。这类信息显然与我们可以多精确地测量肌钙蛋白的水平有关。当我们考虑早期的诊断方法并更改标准并能够重新分层时，我们实际上可以检测到正常浓度这一事实也非常重要。这只能通过高灵敏度测定来完成。因此，在后面的幻灯片上，你可以看到 2009 年的两份出版物，一份在《新英格兰医学杂志》上，一份在《临床化学》上。以及 Keller 等人在《新英格兰医学杂志》上非常重要的出版物，他们是来自 Stefenblankenburg 的小组，看的是西门子 Ultra 分析法。这不是高灵敏度分析法。这是一种很好的分析法，但它不是高灵敏度的分析法。这是西门子的 Ultra 分析。西门子现在也有高灵敏度的检测方法。但是在 2009 年的时候，这是传统的分析方法。你可以在这里看到，99 百分位数。实际上，你知道他们测量了近四千个人。这些人中绝大多数的浓度都检测不到。现在，这与高灵敏度测定相比如何？现在这是我们与贝克曼库尔特合作的原型版本。现在你可以看到此处附近某处的检测有限。我们实际上可以看到存在一种很好的分布。我们能够测量绝大多数人的肌钙蛋白。而且正态分布还不太“高斯”。但是，我们正在接近正态分布，或者至少是可测量浓度。因此，这是高敏的一个非常独特的特性，我们将能够在绝大多数人中测量肌钙蛋白。

So our recommendation for in the Clinical Chemistry, the joint effort by the AACC academy and IFCC committee, was the fact that used to find reference population to report a 99th percentile concentration according to sex specific cutoffs. Obviously this recommendation is not relevant for contemporary assays. The reason for that is as mentioned previously contemporary assays are unable to measure troponin in vast majority of individuals, so you really can't see a difference between males and females. However with high-sensitivity asssay, it becomes very apparent in those healthy individuals that there is a difference in concentrations between males and

females. So part of laboratory recommendations are to obviously report high-sensitivity assays per sex-specific 99th percentiles. This has been obviously also endorsed by the fourth universal definition of myocardial infarction in 2018. And as you can see here, the rationale also being at significantly lower values are observed among women compared with men. And therefore sex-specific 99th upper limits of normal are recommended for high-sensitivity assays. So biology tells us there's differences in the healthy state. The issue is that some of the clinical studies have been performed to date haven't really seen a net clinical benefit and so this is where there's also caveat that there is a controversy as to whether this approach provides valuable additional information for all high-sensitivity assays. So there's more work in this area that is ongoing and more data will be coming out to really flesh out the role of sex-specific 99th percentiles with the respect to patient's outcomes.

因此，在 AACC 学院和 IFCC 委员会的共同努力下，我们在临床化学中的建议是，找到参考人群根据性别特定临界值报告 99 百分位数的浓度。显然，该建议与传统测定无关。如前所述，其原因是传统测定无法测量绝大多数个体中的肌钙蛋白，因此你真的看不到男性和女性之间的差异。然而有了高灵敏度分析，在那些健康个体中，男性和女性之间的浓度差异就变得非常明显了。因此，实验室建议的一部分显然是要根据特定性别的 99 百分位数报告高灵敏度检测方法。显然，2018 年第四次心肌梗死统一定义也认可了这一点。正如你在此处看到的那样，女性与男性相比的理论依据也明显较低。因此，对高敏检测建议用特定性别 99 正常上限。生物学告诉我们健康状态存在差异。问题在于，迄今为止已经进行的一些临床研究并未真正看到临床上的净收益，因此此处还存在一个争议，即该方法是否为所有高敏检测提供有价值的附加信息分析。所以该领域正在开展更多工作，并且将有更多的数据出来，以真正充实特定性别的 99 百分位数在患者结局方面的作用。

So how does one perform a quote-unquote 99th percentile reference population, or determination of 99th percentile in reference population? This is a very challenging task that vast majority of laboratories are unable to do. And here's a publication in the March issue 2020 in Clinical Chemistry that looks at the actual universal sample bank from AACC. And I see nicely describes how the patients were identified and patients were excluded, how other biochemical parameters were used to also screen out individuals, perhaps sub-clinical disease. And so what you can see here that from you know 850 individuals, but 150 of them are excluded, even though they're healthy and they walk in and donate blood. But 150 are excluded due to mostly in the fact that they actually have some obviously issues in regards to biochemical abnormalities. So when you actually this type of process has been documented in literature and even though the 2018 recommendations provided some guidance on how do you derive and develop and kind of assess a population to see whether it's normal and if it's healthy enough in order to measure and interpret and derive the limits for 99th percentile and so forth. There is still a lot of variability in regarding to a patient population. So this is also a street on the right side of this graph where you see that actually there are different levels and these are all different troponin, high-sensitivity troponin assays. And the one thing that just probably I just want to highlight the fact that, here's the overall population of the top if we just look at the fact that say members are females one can also see that here's an example of one high-sensitivity assay that male

concentrations are significantly higher, 99th percentile compared to females. This is typically evidence for all the high-sensitivity troponin assays. However, it is important to notice that how you define your population and what criteria you use to develop and refine your 99th percentiles, including statistical analyses will greatly impact on the values that derive upper limit of normal or upper reference limit when assessing the 99th percentile.

那么，如何进行所谓的 99 百分位数参考人群，或如何确定参考人群中的 99 百分位数呢？这是一项非常具有挑战性的任务，绝大多数实验室都无法做到。这是《临床化学》2020 年 3 月的出版物，着眼于 AACC 的实际通用样品库。我看到了很好地描述了如何识别患者和排除患者，如何使用其它生化参数来筛查个体，可能是亚临床疾病。从这里你可以看到 850 个人，但其中 150 个被排除在外，即便他们很健康并且走进去献血。但是排除了 150 个，主要是因为他们实际上在生化异常方面确实存在一些明显的问题。所以实际上在文献中已经记录了这种类型的过程，尽管 2018 年的建议为你如何推导和发展以及如何评估人群提供了一些指导，以判断其是否正常以及是否足够健康以进行测量和评估，解读并得出 99 百分位数的限制等等。关于患者群体，仍然存在很多变异。这是该图右侧的部分，你会看到实际上存在不同的水平，并且这些都是不同的肌钙蛋白，高灵敏度肌钙蛋白测定。我可能想强调的一件事是，这里是顶端的整体人群，如果我们只看成员是女性这一事实，也可以看出这是一种高灵敏度测定的例子，99 百分位数，男性的浓度明显更高于女性。这通常是所有高灵敏度肌钙蛋白测定的证据。但是，重要的是要注意，在评估 99 百分位数时，如何定义人群以及你用什么标准来开发和完善 99 百分位数，包括统计分析，将极大地影响得出的正常上限或参考上限的值。

So to kind of illustrate that point. Here's just some ratios that were provided from ovbiously from guideline recommended healthy populations from the AACC, and also sample bank, and basically that 99th percentile was divided by the manufacture 99th percentile. So if there was a hundred percents or agreements between what was deriving AACC universal sample bank as opposed to manufacture 99th percentiles. The ration would be one. So as you can see the vast majority of assays, the 99th percentiles are very different from the US AACC universal sample bank as compared to manufacturer's. So again this is kind of highlights the importance of that laboratories need to look at the 99th percentile and determine how it was derived, if it's applicable for your population, or if you're deriving a 99th percentile from healthy individuals that you provide and you perform appropriate analyses to see whether or not it's applicable to your population. And so this is just again illustrates that the 99th percentile has been very important and it's important to use in order to identify myocardial injury. But there is variation in regarding to the reporting and clinical use of 99th percentile.

所以就是说明这一点。这只是从 AACC 以及推荐的样本库中根据指南推荐的健康人群提供的一些比率，基本上是将 99 百分位数除以制造商的 99 百分位数。所以如果 AACC 通用样本库的来源与制造 99％的样本之间存在 100％的一致。比率就是一。因此，正如你所看到绝大多数检测方法，制造商的 99 百分位数相比于美国 AACC 通用样本库有很大不同。因此，这再次凸显了其重要性，实验

室必须了解 99 百分位数并确定其获得方式，是否适用于你的人群，或者你是否是从提供的健康个体中获得 99 百分位数。进行适当的分析，以了解它是否适用于你的人群。因此，这再次说明了 99 百分位数非常重要，因此使用它来识别心肌损伤也很重要。但是关于使用 99 百分位数的报告和临床使用方面存在差异。

So again, majority of assays, a majority of laboratories are unable to determine or to derive a reference upper limit of normal with 99th percentile to really assess if, you know, healthy individuals, both men and women have concentrations above the limit of detection. And so that was the recommendation five and our joint recommendation documents that in order to define a high-sensitivity assay that troponin concentrations at or above the limit of detection at least fifty percent of healthy women and sort of healthy men and women. And if they don't get that then we would perhaps consider the most contemporary assays. But again this is very difficult for laboratories in order to obtain large healthy populations to assess measurements. And so one alternative approach that may be of uses, in fact that other sites that can perform reference population testing for determing, or perhaps even LoD testing, we'll talk about that in a little bit, perhaps one other thing one could do is that the fact actually determine or measure a quality control material below 10 ng/L. So by the vast majority of high-sensitivity assays, compared to contemporary assays, a general rule, you know, most of the contemporary assays have a lower limit of 0.01 and high-sensitivity assays, or 0.01 micrograms per liter which is equivalent to ten nanograms per liter. So vast majority of conventional assays are unable to measure concentrations below ten nanograms per liter or below 0.01 micrograms per liter, whereas high-sensitivity assay can. So there is actually some published criteria regarding allowable bias as well as precision estimates below 10 nanograms per liter which could be used for sites that are adopting and utilizing high-sensitivity assay. So perhaps not every lab can actually you know derive the upper limit of normal and 99th percentile or obtain a large sample size of healthy individuals with the appropriate exclusion criteria to assess the true nature of that assay being a high-sensitivity assay. But one thing that laboratory, all laboratories can do is actually measure concentration below ten nanograms per liter or below the 99th percentile in order to see whether or not it meets acceptable analytical performance.

同样，在大多数检测方法中，大多数实验室都无法确定或得出 99 百分位数的正常参考上限以真正评估健康个体，无论男女，的浓度是否都高于检测限。因此，这是建议 5 和我们的联合建议文件，为了定义一种高灵敏度测定法，肌钙蛋白浓度应达到或超过至少能检测 50％健康女性以及稍稍健康的男性和女性的限度。如果他们不了解，那么我们可能会考虑采用最传统的检测方法。但是同样对于实验室来说，要想获得大量健康的人群来评估测量结果，这是非常困难的。因此有一种可能有用的替代方法，实际上其他可以进行参考人群检测以确定或者甚至是 LoD 测试的站点，我们将稍作讨论，也许另一个可以做的是确定或测量一个低于 10 ng/L 的质控材料。因此，与传统测定法相比，对于绝大多数高灵敏度测定法，一条总则是大多数传统测定法的下限为 0.01，而高灵敏度测定法，是每升 0.01 微克，相当于 10 纳克/升。因此，绝大多数常规测定无法测量低于 10 纳克/升或低于 0.01 微克/升的浓度，而高灵敏度测定却可以。因此，实际上存在一些有关允许偏差的标准，以及低于 10 纳克/升的精确度估计值，这些标准可用于使用高灵敏度测定法的站点。因此，也许并非每个实验室实际上都可

以得出正常值上限和 99 百分位数，或者使用适当的排除标准来获得一个大样本量的健康个体，以评估该检测的真实值，就是高灵敏度检测。但是实验室，所有实验室可以做的一件事实际上就是测量低于 10 纳克/升或低于 99 百分位数的浓度，以判断其是否达到可接受的分析性能。

So, and this leads to our recommendation one: for high-sensitivity assays, laboratories should measure at least 3 different concentrations of quality control materials. And most importantly when we think about that, again we want to report nanograms per liter for quality controls, we always report one decimal place; for patients, we report in whole numbers. But for quality control, we're gonna do one decimal place. And most importantly, the one level of quality control material that we've advocated laboratories to do is measure user concentration between the limit of detection and the lowest sex-specific 99th percentile. So for most instances, that's below the female 99th percentile. So this is actually a normal concentration, so that's one thing that laboratories can do. And if you're able to measure a high-sensitivity assay in the normal range of appropriate precision, you should feel comfortable, and you should be confident on the utility of that assay and its proposed clinical benefits for patients as well.

因此，这就是我们的建议一：对于高灵敏度测定，实验室应至少测量 3 种不同浓度的质量控制材料。最重要的是，考虑到这一点，我们再次希望报告每升纳克的质量控制，我们总是报告小数点后一位。对于患者，我们则报告整数。但是对于质量控制，我们将保留一位小数。最重要的是，我们提倡实验室进行的质量控制材料的一个水平是，在检测限和最低性别特定百分位数之间测量用户浓度。因此，在大多数情况下，其低于女性 99 百分位数。因此，这实际上是正常的浓度，因此实验室可以做这件事。而且，如果你能在适当精度的正常范围内进行高灵敏度测定，你应该感到舒服，并对这种测定的效用及其对患者的临床获益充满信心。

So what does that mean when we actually measure a quality control material down below 99th percentile or normal level. So this slide just highlights the fact again, we manufacture on quality control material for last number of years and here I want to illustrate three different materials that we've manufactured. And what's important here is that we look at two different laboratory sites. And so what we've seen in period of nearly two years is that laboratory one was actually measuring differently than laboratory two. Again very similar, this would be close to 4 and this would be close to 5.5 or close to six. So there is little bit of offset here and why that's important is that there are some algorithms that use a common low cutoff in order to, perhaps identify patients at low risk or perhaps could be used to read out a MI. And that's OK, if it's just at one hospital. But if there are two hospitals in your system and the assyas are running this different apart and it comes very difficult to see what's the most appropriate cutoff because again one and one sites running differently than the other. However as you can see over the period of years, the two analyzers at two sites actually became greater agreement with each other. So now obviously from 2017 to May 2019 we can see that both site one analyzer one and analyzer two are running equivalently at this level. And again, we kind of support, the fact now we probably

can use a common cutoff and report that and use that and clinicians could feel more comfortable of acceptable and agreement between analyzers and sites because we are actually now achieving the same type of precision, the same type of measurement performance. So again without actually measuring quality control material below the 99th percentile of the normal range, laboratories were not be able to inform clinicians whether or not you know there's agreement at lower end which again can be used for early decision making.

因此，当我们实际测量低于 99 百分位数或正常水平的质量控制材料时，这意味着什么？这张幻灯片再次强调了这一事实，我们在过去几年中制造了所使用的质量控制材料，在这里我想说明一下我们制造的三种不同材料。在这里重要的是我们要看两个不同的实验室站点。因此，我们在近两年的时间里看到，一号实验室的测量实际上与二号实验室的测量有所不同。同样非常相似，这里接近 4，这里接近 5.5 或接近 6。因此，这里没有什么偏移，为什么这里重要，是有些方法使用共同的低临界值以识别低风险患者或者可被用来读出 MI。但如果只是在一家医院就没关系。但是，如果你们系统中有两家医院，而检验分开运行，那么很难确定最合适的临界值，因为一个站点和另一个站点的运行不同。但是，正如你所看到的，在过去的几年中，两个站点的两个分析仪实际上彼此之间变得更加一致。现在，从 2017 年到 2019 年 5 月，我们显然可以看到站点一的分析仪一和站点二的分析仪在此水平上均等效运行。又一次，我们好像有了些支撑，事实是我们现在可能可以使用一个通用的临界值并进行报告，并进行使用。而临床医生可以更轻松地接受分析仪和现场之间的一致性，因为我们实际上已经达到了相同的精度，相同类型的测量性能。因此，没有实际测量低于正常范围 99 百分位数的质控材料，实验室就无法告知临床医生在低水平的一致，而该水平可被用于进行早期决策。

So is this just relevant for one assay, well know it's relevant for majority of high-sensitivity assays that you're able to monitor the assays using the low concentration or low normal concentration as well as one near the 99th percentile. So here we did a comparison between Abbott high-sensitivity troponin I versus Beckman's high-sensitivity troponin I. Here we see concentrations, we receive a low normal concentration 5.1 with the Abbott at one of our sites, whereas at Beckman it's gonna be a little difference, 3.9. But importantly the precision and the SDs both of these sites and both these levels are acceptable for performance SDs as 0.8 or lower. And here Edmonton Beckman at 0.3. So again one can measure a low normal concentration of a high-sensitivity assay, achieve appropriate position goals only when using a high-sensitivity assay. And then when you look at a concentration near the male 99th or near the overall 99th percentile, one can also achieve to realize acceptable very tight precision well below ten percent with, as you can see, with the Abbott assay, and as well with the Beckman assay. So for example, 23.6 with a SD of 1.0, CV4.2%. So again, analytical performance for high-sensitivity assays, if you use the recommendations and using a normal concentration for quality control as well as one near the 99th percentile or upper 99th percentile, in which case most of that are males at 99th percentile. You can actually achieve excellent analytical performance. So this is something that should provide confidence for laboratories for releasing and reporting results of high-sensitivity assays.

那么这仅是与一种测定有关，众所周知，它与大多数高灵敏度测定有关，因此你可以使用低浓度或低正常浓度以及接近 99 百分位数来对检验进行监测。这里我们对雅培高敏肌钙蛋白 I 与贝克曼的高敏肌钙蛋白 I 进行了比较。在这里我们看到浓度，我们在其中一个位点使用雅培时得到了 5.1 的低正常浓度，而在贝克曼有点差异，3.9。但重要的是，对于性能标准差为 0.8 或更低，这两个站点以及这两个水平的精度和标准差都是可以接受的。这里是贝克曼的 Edmonton，是 0.3。所以可以测量高灵敏度测定法的正常低浓度，仅在使用高灵敏度测定法时才能达到合适的位置目标。然后，当你看男性 99 百分位数附近或整体 99 百分位数附近的浓度时，也能达到实现可接受的非常窄的精读，远低于 10%，如你所见，用雅培分析法以及贝克曼分析。若依例如，23.6，标准差 1.0，CV4.2％。同样，高敏分析法的分析性能，如果你应用建议并使用正常浓度进行质量控制以及一个靠近 99 百分位数或上 99 百分位数，在这种情况下，大多数 99 百分位数的男性。你实际上可以达到出色的分析性能。因此，这应为实验室发布和报告高灵敏度测定结果提供信心。

However, it’s important to note that this is sometimes a challenging endeavor and sometimes a problem could be with a quality control material and not necessarily your assay. So you wanna be mindful on selecting quality control material that is benefits to your assay and to your laboratory. So here's an example where we, here's our patient pool near the 99th percentile. Here we see again, the mean at 34, CV is 3.2%, so this is near the, for the Abbott assay, near the male 99th percentile, so excellent performance with a CV of 3.2%. So at the same time we measure another quality control material at the same time. And so what we see here is obviously the concentrations a little different. I want to draw your attention to is the CV has increased. So the impresion with quality control material, the commercial quality control is actually higher than it is on the patient pool material. And so this wasn't just, you know, this was obviously evident while we did a crossover, so this was also evident when we went with this quality control material to see afterwards we see the same types of imprecision state, 7.5%. And this is just not obviously specific for one assay. When we use another high-sensitivity assay, we also achieved somewhat sub-optimal precision estimates. So it is important to laboratories, you know, selective proper quality control material, know that sometimes the imposition sources sometimes may be overstated or perhaps could look worse than what it is for patients. But the fact of the matter is laboratories need to monitor their assays at the lower end as well as obtain proper quality control material and appropraite rules so that we can mitigate any aalytical variations that could impact on patient outcomes.

但请务必注意，有时候这是一项艰巨的尝试，有时质控材料可能会出问题，而不一定是你的检验。因此，你要谨慎选择对分析和实验室都有利的质控材料。这里有一个例子，这是接近 99 百分位数的患者库。这里我们再次看到，均值 34，CV3.2％，对于雅培检测，这接近男性 99 百分位数，CV3.2％时表现出色。而我们要同时测量另一种质量控制材料。我们在这里看到的浓度显然有一点不同。我想请你们注意的是 CV 有所增加。所以是质控材料的不精密度，实际上是商业质控要比患者库材料更高。显而易见，当我们进行交叉时，这是显而易见的，当我们用这种质控材料之后，我们看到的是相同类型的不精密度，7.5％。而且这显然不只是一种测定方法。当我们使用另一种高灵敏度测定法时，我们

也获得了一些次优的精度估计。因此对于实验室来说，选择合适的质控材料非常重要，要知道有时固定来源可能被夸大了，或者看上去可能比用在患者身上差。但事实是实验室需要在低水平端监控其测定，并获得适当的质控材料和适当的规则，从而我们减少可能影响患者预后的任何分析差异。

So the other recommendation that we made in the joint document was that when sites go to a high-sensitivity assay that they should at least validate or look at the LoD and the LoB. And again this is not necessarily applicable worldwide presently FDA only allows reporting down the limit of quantitation. So how would one go about doing this regards to perhaps, you know, assessing is my low end appropriate, am I really reporting undetectable concentrations if, you know, measuring a sample with no known analyte. So I think it's really not a trivial matter and the fact that there's gonna be variation and differences on what materials are used in assessing the lower limit of reporting. So here's an illustration with three different high-sensitivity assays. Where for example we want to determine what the lower limit of the blank was so this is a material without any troponin. So one material that doesn't have any troponin in this water. And so if you run water sixty times on the Abbott assay, you get 0.6 ng/L and that’s the LoB. So again this is the noise, it's related to just material without any analyte. So I think we'd all agree water doesn't have any troponin, but what you actually start to measure water on different high-sensitivity assays, you're starting to see some measurable concentrations. So one may question wow, maybe these are not high-sensitivity assays. That's not really the case. The fact of the matter is that majority and most of the high-sensitivity assays over number of years have been reformulated to obviously determine demand of protein that’s in a patient sample and they've optimized the testing to replicate what's in the patient samples. So obviously patients don't have water running through them, they are actually plasma and in plasma there's a lot of protein and so forth and so on. So when you actually do use a more appropriate material, for example, Beckman, if you use the sample diluent, you get a very reasonable LoD of 0.5. For the Siemens EXL assay, if you use a zero caliborator, you get a very low LoB of 0.9. So again, one thing that laboratories could do is the fact that you know you may want to make sure that your assay performs well and we make recommendations as well so you want a yearly check it and challenge the low end is really reporting undetectable concentrations. If you can't use water to do non specific binding, then you may want to assess the sample diluent. And if that doesn't work then you won't look at zero caliborator. So one time labs should be at least monitoring assessing that indeed they are able to report undetectable concentrations, but the rate in the way that labs do that actually depends on the high-sensitivity assays that they use.

因此，我们在联合文件中提出的另一项建议是，当站点进行高灵敏度测定时，他们至少要验证或查看 LoD 和 LoB。同样，这不一定在全球范围内都适用，目前 FDA 仅允许报告定量下限。所以该怎么做呢，合适评估我的低水平，我有没有报告无法检测浓度，大家懂得，就是测量没有已知分析物的样品。所以我认为这确实不是一件细碎的事，而且在评估报告下限所使用的材料上也会有变异和差异。这是使用三种不同的高灵敏度测定法的说明。例如，我们要确定空白的下限是多少，所以这是不含任何肌钙蛋白的材料。这水里没有含任何肌钙蛋白的物质。因此，如果你在雅培分析中测试六十次水，你会得到 0.6 ng/L，这

就是 LoB。同样这就是噪声，它与没有任何分析物的材料有关。所以我认为我们都同意水不含任何肌钙蛋白，但是实际上你在不同的高灵敏度测定中开始测量水时，就会开始看到一些可测量的浓度。因此，有人可能会对此表示质疑，也许这不是高灵敏度的检测方法。事实并非如此。事实是，经过多年重新设计，大部分和大多数高灵敏度测定法可以明确确定患者样品中的蛋白质，并且他们已经优化了测试以复制患者样品中的发现。显然患者身上流的不是水，他们实际上是血浆，血浆中有很多蛋白质，各种各样。因此，当你实际使用更合适的材料，例如贝克曼时，如果使用样品稀释液，则 LoD 值就非常合理，是 0.5。对于西门子 EXL 分析，如果使用零校准品，则 LoB 值非常低，为 0.9。同样，实验室可以做的一件事是，你可能希望确保自己的测定性能良好，我们也会提出建议，因此你希望每年进行一次检查并挑战低水平端，这实际上是报告了不可检测的浓度。如果你不能用水进行非特异性结合，那么你可能需要评估样品稀释液。如果那不起作用，那么你就不会用零校准品。因此，实验室应该至少进行一次监测，以评估它们确实能够报告无法检测到的浓度，但是该方法实际上取决于他们使用的高敏测定。

So I'm going on to objective three, what are some of the strengths and weaknesses possibly of earlier testing protocols for high-sensitivity cardiac troponin testing in the emergency department. So again this was nicely highlighted in 2015 ESC Guidelines, where data mainly from the base study group and important studies have been done out of the europe multicenter studies. They've devised a very early rule-in and rule-out algorithm where troponin can be measured over a period of one hour in order to either rule out patients or rule in patients for mild cardiac infarction. So again at the time of this publication only two assays were actually had regulatory approval. I would not focus on this assay down here, cause that was just a research assay at the time. So how would this work? So for example they have Roche troponin T assay and Abbott troponin I assay. So I'll just focus on the Abbott troponin I assay because they are obviously different companies that have also have their 0/1 algorithm to derive from that I'm all looking at troponin I. So how does this work. So patient comes in with a clinician and all sorts of clinicians, a clinical suspect that the patient and believe there could be possibly some symptoms suggestive of acute coronary syndromes. And they're going to measure troponin. So in this algorithm for Abbott assay, if the zero hour troponin is below 2 ng/L, you can rule out MI. And or if their zero hour the presentation sample is less than five and the change between 0/1 hour is less than two you can rule out. So here's an example of that can be used for Abbott assay. And I'll be on the opposite side to rule in if the patient comes in with very high values greater or equal to 52 or a change of 6 ng/L over one hour, you can rule in. So these have been validated and they're used throughout Europe and across the world. And now we can see that there's algorithm for the Abbott assay and obviously troponin T for Roche. What we see the results for Siemens, the Beckman assays and the Ortho assay. So these are very much some clinicians like these approaches because they can use this for early decision-making in the ED. In the laboratory, one thing you want to be mindful of this is how robust are these criteria, how robust is a less than two to rule out, how robust a change of two to rule out or a change of six to rule in. And so these are important information that a laboratory should be doing in assessing so they can provide some when being consulted from clinicians, they can

provide some evidence and some advice in regards to changes at low end. Because these are all absolute changes that they used for early decision making.

我下面探讨目标三，即急诊室中用高敏感性心肌肌钙蛋白测试的早期测试方案可能有哪些优缺点。2015 年 ESC 指南中有很好的强调，该指南中的数据主要来自基础研究小组和重要的研究，而这些数据来自欧洲多中心研究。他们设计了一种非常早期的纳入和排除方法，可以在一个小时内测量肌钙蛋白从而纳入患者或排除患者患有轻度心肌梗死。所以在本出版物发布时，实际上只有两种检测方法获得了监管部门的批准。我不会在这里重点介绍这种分析方法，因为当时这只是研究方法。那么这是怎么工作的？例如，他们有罗氏肌钙蛋白 T 检测法和雅培肌钙蛋白 I 检测法。好的，我只关注雅培肌钙蛋白 I 的检测，因为它们显然是不同的公司，它们的 0/1 方法也可以从中得出。所以这是如何工作的。患者来了，临床医生和各种临床医生，临床上怀疑患者，并认为可能存在一些可能提示急性冠状动脉综合征的症状。他们要测量肌钙蛋白。这里的方法，用雅培分析，如果零小时肌钙蛋白低于 2 ng/L，你就可以排除 MI。并且或者如果他们的零小时样品不到 5，并且 0/1 小时间的变化小于 2，则可以排除。这里有一个例子，其可用于雅培分析。我到另一侧来纳入，如果患者来了，值非常高，高于或等于 52 或是一小时的变化超过 6 ng/L，你就可以纳入了。所以这些都已经过验证并且在整个欧洲和世界各地都有使用。现在我们可以看到，有用于雅培分析的方法，显然还有罗氏的肌钙蛋白 T。我们看到的是西门子，贝克曼分析和奥森多分析的结果。有一些临床医生喜欢这些方法，因为他们可以将其用于急诊的早期决策。在实验室中，你需要牢记的一点是这些标准的有多强，2 以下排除有多强，2 以下排除或变化为 6 就纳入，有多强。 因此，这些都是实验室在评估时应该做的重要信息，以便它们可以在临床医生咨询时提供一些信息，它们可以提供有关低端变化的一些证据和建议。因为这些都是用于早期决策的绝对改变。

So the first thing that laboratory to be mindful of is that there is definitely variation near the lower limit of reporting. So here's a publication, in Clinical Chemistry, we look to external quality assurance testing. So this was with the Abbott assay, so at the ESC cutoff of 2 ng/L in order to rule out MI with the Abbott assay. So there were about thirty sites, this was almost a fifty-fifty split. So sixty percent of sites reported less than two and forty percent reported two or more. And you can see that in this type of diagram were, for example we have some sites that were reporting at two or less than two and then we see some nice variations above them. Importantly even though they are high-sensitivity, some assays have reported less than ten. So again clinically, it’s important that laboratory properly reports high-sensitivity troponin assays, use the right lower limit of reporting, because clinicians could be easily confused to say, well you know, my troponin undetectable and I can send them home. In this site, if they use it less than ten, that's inappropriate. In fact, as we know there's perhaps measurable concentration in that patient. So more appropriate aspect is reporting down to a lower limit of detection if it’s all possible. But again even here we’ll see that there is variation. So there's nothing that can be done here for the most part but it's important you relay that information to clinicians for patients, say with Abbott assay comes at 2, it’s a flip of a coin if it's really 2 or below 2.

因此，实验室首先要注意的是，在报告下限附近肯定存在差异。这是《临床化学》杂志上的出版物，我们将进行外部质量保证测试。这是使用雅培测定法进行的，在 ESC 临界值为 2 ng/L 时，用雅培测定法排除 MI。所以大约有三十个点，这几乎是五五对半。所以百分之六十的点报告小于 2，百分之四十的点报告 2 或更多。你可以看到，在此类图中，例如，我们有一些站点的报告数量为 2 或不到 2，然后在它们上面我们看到了一些不错的改变。重要的是，尽管它们是高敏，但一些分析报告还不到 10。因此，从临床上来说，实验室必须正确报告高敏感度肌钙蛋白检测结果，并使用正确的报告下限，因为临床医生很容易混淆，说我的肌钙蛋白无法检测，我可让他们回家。在这个点，如果他们用的不到 10，则是不合适的。实际上，据我们所知，该患者的浓度可能是可测量的。因此，如果可能的话，更合适的是将检测报告降低到最低限度。但是即使在这里，我们也会看到变异。因此，在这里大部分事情是无能为力的，但重要的是将这些信息传达给患者的临床医生，比如说雅培检测值是 2，那么到底是 2 还是 2 以下，其实就是抛硬币。

So the other thing the laboratories need to be mindful again using these algorithms at low troponin concentrations are obviously the variability of which is just highlighted, but another thing that we need to assess is interferences. So here's a publication back in 2010, where the investigator looked at the effects of hemolysis on troponin T concentration. Now on the ESC 0/1 algorithm, if the patient’s sample is less than five, they can be ruled out. So here's a concentration at 6 ng/L, now you can see a little bit of hemolysis in that sample. It’s forty percent decrease in troponin T concentration. So again what was a fix and what would have placed the individual possibly in the observation zone, perhaps when it be ruled out at the admission sample. If that sample was hemolyzed, it would drop below five to a bit of 4 ng/L, so they can be ruled out. So again, it's important that laboratories look at that aspect, and if there is a hemolysis or an interference that could impact the concentrations of low end that laboratories appropriately report that information to clinicians so that there's no patient classification. However it's very important that these types of interference studies are just not generalized statement that hemolysis leads to lower concentrations. It has to be assessed per assay. So here you can see that if you look at two high-sensitivity troponin assays, they are with different concentrations of hemolysis and really there is no appreciable effect at low concentration of troponins that should below normal concentrations of five or three or what have you, you’ve seen no differences. And that's for hemolysis and that’s for icterus. So this is important that laboratories do assess or at least make note of the fact do these common interferences, hemolysis or icterus, do they impact interpretations or do they impact local variation of the low end.

所以实验室在低肌钙蛋白浓度下使用这些方法时需要再次注意的另一件事显然是可变性，刚强调过，但我们需要评估的另一件事是干扰。这是 2010 年的出版物，研究人员研究了溶血对肌钙蛋白 T 浓度的影响。现在使用 ESC 0/1 方法，如果患者的样本不到 5，则可以将其排除。这里的浓度为 6 ng/L，现在你可以在该样品中看到一点溶血现象。这是肌钙蛋白 T 浓度降低 40％。如此一来，什么是确定的，以及什么会使以个人可能进入观察区，也许是在入院时样本被排除的情况下。如果该样品溶血，它将降至 5 以下，4 ng/L 多一点，因此可以将其排除。因此，更重要的对于实验室应从这一方面着眼，如果存在溶血或干扰

可能影响低端浓度的情况，实验室应适当地将该信息报告给临床医生，以便进行患者分类。但是，非常重要的一点是，这些类型的干扰研究不是概括性地说溶血导致浓度降低。一定要对每个测定法进行评估。多以在这里你可以看到，如果你看两种高敏感度肌钙蛋白测定法，它们的溶血浓度不同，并且实际上在低浓度的肌钙蛋白，低于正常浓度 5 或 3 或以下时没有明显影响，你没有看到任何差异。溶血如此，黄疸亦然。因此，重要的是实验室必须评估或至少注意以下事实：这些常见的干扰，溶血或黄疸，影响解释或影响低水平的局部变异。

The other thing that is obviously been highlighted even in the earlier recommendations is that you don't want to use different sample types. So it's really important that laboratories only accept one sample type when patients are being evaluated for say, a patient having acute myocardial infarction. And the reason as follows is that there are sometimes differences between different sample types. So on this example, the Abbott assay, what we observed in this study was the fact that troponin was proportionally higher at higher concentrations. With the Abbott assay, it is compared to EDTA plasma. So again highlights of the fact is that you just want to keep the same sample type because clinicians are looking for changes in concentrations, some of that is absolute, some of that is percentage or relative. Needless to say you don't want to have a heparin plasma on the same patient. You don't want a EDTA plasma one time and a heparin plasma at the second time measurement because you'll see variations due to the sample matrix and not necessarily anything to do with the changing of the patient’s concentration of troponin. So again it's really important that laboratories only accept one sample type while testing especially for patients in the acute care setting.

在之前的建议中，要强调的另一件事是你不想使用不同的样本类型。所以在对患者进行评估时，例如患有急性心肌梗死的患者，实验室仅接受一种样本类型是非常重要的。原因如下：不同样本类型之间有时会存在差异。因此，在本例雅培分析中，我们在这项研究中观察到的事实是肌钙蛋白在较高浓度下成比例地较高。用雅培分析，将其与 EDTA 血浆进行比较。因此另一个亮点是你只想保持相同的样本类型，因为临床医生在寻找浓度的改变，其中有一些是绝对的，有一些是百分比或相对的。不用说，你不想在同一名患者身上用肝素血浆。你不想一次使用 EDTA 血浆，而在第二次用甘肃血浆，因为你会看到由于样品基质而引起的变化，而不一定与患者肌钙蛋白浓度的变化有关。真正重要的是实验室在测试时仅接受一种样本类型，特别是针对急诊患者。

Well, are there other things that can cause variations in classifications of cardiac troponin? And one of the things that we've observed and this was published in 2018 and this is for many different high-sensitivity assays, Abbott, Beckman and Roche. So when we did the comparison between Abbott and Beckman and we did several different measurements. So here's the Abbott high-sensitivity that was clinically reported and we take the samples and measured it. Again for the Abbott assay and again for the Beckman assay on the axis too. So we see that there's reasonable agreement between the assays. However there are a number of patients where Beckman reported significantly lower results than Abbott and I just want to highlight

patient one. So patient one came in with syncope. This is the concentration of the times of draws for the Abbott high-sensitivity troponin assays. So here we receive a fifteen hundred and then it went to thirteen hundred then it went to thirteen fifty four. So sample number one was we obtained at this time frame thirteen fifty four, 1354 ng/L. When we repeated it on another analyzer of the Abbott assay, we had 1447. But surprisingly when we ran that sample with Beckman assay, it was only a twelve. So this is well below the 99th percentile and obviously this was a male that was below the male 99th percentile. So when we measured on the Roche, we got a sixty five. What we actually ended up doing was doing a PEG precipitation cause we're suspecting perhaps this could be a macro complex and there's two types of macro complexes. But for the majority of the troponin assays when we think of macro complexes, we think of immunoglobulin based complexes are formed. So we did a PEG precipitation measured on the Abbott assay. We see that the result now is only 4. So it was only 0.3% of recovery. Typically less than 20%, you would say there's a macro present and then we actually measured CK-MB on the earlier sample. We actually obtained a normal result. So here's an example where we can get very different results and clinicians will have to do serial measurements and aren't seeing any changes. And part of the reason for the discrepancy or lack of change may be due to a macro complex, which may not be what a patient came in and may not be due to an acute condition. So again macros could produce wildly different results and something that laboratories need to be aware of its infrequent but they could occur.

好吧，还有其他事情会导致心肌肌钙蛋白分类的变化吗？我们观察到的一件事是于 2018 年发布的，是用于许多不同的高灵敏度测定法，雅培，贝克曼和罗氏。因此，当我们在雅培和贝克曼之间进行比较时，我们进行了几种不同的测量。这是临床上报的雅培高灵敏度产品，我们拿了样品并进行测量。对雅培分析和对贝克曼分析，在轴上。所以我们发现这些分析之间存在合理的一致性。但是有许多患者的贝克曼报告的结果明显低于雅培，我只想强调一个患者。一号患者来，伴有晕厥。这是雅培高灵敏度肌钙蛋白测定的抽血时间的浓度。这里是 1500，然后到 1300，然后到 1354。所以样品一是在此时间框获得，1354，1354 ng/L。当我们在另一种雅培分析仪上重复该分析时，我们得到的是 1447。但是令人惊讶的是，当我们用贝克曼检测该样本时，它只有 12。因此，这远低于 99 百分位数，而且很明显这是个男性，低于 99 百分位数。当我们在罗氏上进行测量时，我们得到了 65。我们实际上最终要做的是进行 PEG 沉淀，因为我们怀疑这可能是一个大复合物，并且有两种类型的大复合物。但是对于大多数肌钙蛋白测定，当我们想到大复合物时，我们认为会形成基于免疫球蛋白的复合物。因此，我们在雅培检测上测定 PEG 沉淀。我们看到结果现在只有 4。所以回收率只是 0.3％。一般不到 20％，你会说存在一个大复合物，然后我们实际上在较早的样本上测量了 CK-MB。我们实际上获得了一个正常结果。这里有一个例子，我们可以得到很不一样的结果，而临床医生将不得不进行一系列测量但看不出任何变化。差异或缺乏变化的部分原因可能是由于大复合物，而不是患者进来的原因，也可能不是由于急性疾病。因此，大复合物可能产生截然不同的结果，所以实验室需要注意一些不常见的情况，但它们可能会发生。

Also to illustrate this point was again another publication in the March issue of Clinical Chemistry this year. Lam and colleagues from New Zealand looked at groups

of patients from the community, not in the hospital, that had troponin request to be measured. So there are 241 individuals and of these individuals you know they performed this evaluation to see whether or not there's a macro or not. So at the end of the day it was about one hundred or less than fifty percent of them didn't have a macro, which means that half of those people are the ones that actually had a macro. And so on the right-hand side is an illustration, different high-sensitivity assays. And the author actually came over this nice terminology, when there's a macro complex they call it macro-ick. So this is where there's a macro immunoglobin valent to troponin I or perhaps troponin I-C complex. Macro-tick, which is an immunoglobin valent to all three troponin T-I-C, perhaps one would be degraded. And also there's could just be macro complex for troponin T. But when they looked at say the macro-ick, which is up here, or a macro-tick, which also included troponin T, what they actually observed was that assays that actually had three antibodies n regards to their design in order to detect and measure troponin. What they observed was that there were more, the majority of those assays actually had a higher percentage or a higher number of macro complexes detected. So, for example here we can see a both Siemens assay used three antibodies in design, and close to eighty percent of the samples that patients have concentrations above the 99th percentile, whereas other high-sensitivity assays with Beckman being lower. Beckman also had lower recovery in these macro complexes. So the authors make an interesting observation, perhaps there's higher immuno activity for macro troponin I when using a 3-site antibody based upon these data. So we looked further into this to see if that's really the case.

同样要说明这一点的是今年三月份《临床化学》上的另一份出版物。来自新西兰的 Lam 及其同事研究了社区中而非医院里有肌钙蛋白测定需求的患者群体。共有 241 个人，在这些人中，他们进行了此评估以盼到是否存在大复合物。结果到最后，大约有百分之一百或不到百分之五十的人没有大复合物，这意味着这些人中有一半是实际有大复合物的人。右手边是一个展示，不同的高灵敏度检测方法。作者实际上给出了这个很好的术语，当存在大复合物时，他们称其为 Macro-ick。因此，这就是肌钙蛋白 I 或可能肌钙蛋白 I-C 复合物的大型免疫球蛋白。Macro-tick，一种与所有三种肌钙蛋白 T-I-C 均等效的免疫球蛋白，可能会被降解。而且也可能是肌钙蛋白 T 的大复合物。但是当他们说 macro-ick，或是 macro-tick，其也包含肌钙蛋白 T，他们实际观察到的是实际上为了检测和测量肌钙蛋白设计有三个抗体的分析。他们观察到的是有更多，大多数的分析实际上检测到的大复合物的百分比更高或数量更高。举例，在这里我们可以看到西门子设计的两种检测方法都使用了三种抗体，并且接近 80％的患者浓度高于 99 百分位数，然而贝克曼的其他高灵敏度检测方法则较低。贝克曼对这些大复合物的回收率也较低。因此，作者做出了一个有趣的观察，基于这些数据，当使用 3 位抗体时，也许对大肌钙蛋白 I 的免疫活性更高。多以我们对此进行了进一步研究，以查看是否确实如此。

And so here's an example of a case that was brought to our hospital in regarding to clinicians and cardiologists were assessing whether or not this elevation was due to a macro complex or there's something else going on. So here's a case of a forty year old female, final diagnosis of noncardiac chest discomfort, coronary CT angiography was fine and there's no evidence about atherosclerotic diseases or coronary stenoses. So looks like cardiovascular side is all good. A plasma sample was submitted to the

laboratory to investigate if a macrocomplex was present. Cardiologist suspected it because values were high and unchanging. We performed this via the PEG precipitation. So the initial results on that patient sample that was submitted was 130 ng/L by the Abbott assay after PEG, recovery was less than 0.5%, result was 0.6. So again this is well below 20%, so this was suggestive of macro complex. We took the same sample and measured at the 3-site immunoassay. So for this one we looked at Siemens EXL high-sensitivity assay. Again, 3-site immunoassay the result was again 213 ng/L. So again a high-sensitivity assay, 3-site design yielded higher concentrations of macro. But this is not always the same case. Here, we look at that same sample with Ortho assays, also 3-siteimmunoassay, now yielded a result of 4.5 or normal concentration on that patient sample. So again illustrates the fact that clinicians need to be aware of macros. Laboratories, when they are approached or a consultant regarding the presence of these complexes, they need a plan in place in order to try to rectify and resolve these issues. And it may not be so simple to say that it lies on 3-site assay of courses they have a macro, or maybe the fact is that 2-site assay doesn’t have a macro. There are more factors into play. So one thing that is also the case that there should be some caution that you know the makeup of these complexes is going to be very very different and they're gonna interact differently with all different assays. So at the end of the day laboratories need to be aware of this and if they are approached by a macro, need to be able to provide some evidence provide some interpretation that could be provided to clinicians and also a plan in place to rectify and resolve these issues in the future. You know when these patients re-present what have you that interpretation to be done appropriately.

这是一个例子，是被带到我们医院，临床医生和心脏病专家正在评估这种升高是否是由于大复合物引起的，还是有其他情况。此例为一名 40 岁的女性，最终诊断为非心源性胸部不适，冠状动脉 CT 血管造影良好，没有动脉粥样硬化疾病或冠状动脉狭窄的证据。看起来心血管方面都很好。血浆样品已提交检验科，以调查是否存在大复合物。心内科医生有怀疑是因为值很高并且没有改变。我们是通过 PEG 沉淀进行的。通过 PEG 后的雅培测定，该患者提交的样品的初步结果为 130 ng/L，回收率小于 0.5％，结果为 0.6。因此，这又远低于 20％，因此提示大复合物。我们采集了相同的样品并在 3 位免疫测定中进行了测量。对于这一个，我们看了西门子 EXL 高灵敏度检测方法。再次进行 3 位免疫测定，结果是 213 ng/L。因此，再次进行高灵敏度测定，3 位设计可产生更高浓度的大复合物。但这并非总是一样。这里我们用奥森多检测，也是 3 位免疫测定，看相同的样品，现在对该患者样品产生 4.5 或正常浓度的结果。因此，再次说明了临床医生需要注意大复合物这一事实。当实验室被问及或有关于这些复合物存在的咨询时，他们需要有个计划以尝试改正并解决这些问题。说它是基于对 3 位测定当然会有大复合物，可能不那么简单，或者事实是 2 位分析没有大复合物。还有更多因素在起作用。因此，同样需要注意的是，这些复合物的组成将非常不同，并且它们在所有不同的测定中的相互作用都会不同。所以实验室最终需要意识到这一点，并且如果它们被问及大复合物，则需要能够提供一些证据，提供一些可以提供给临床医生的解释，并在将来准备好计划已纠正和解决问题。这些患者再出现时，你要有合适的解读。

So that was a real life case sample, but what about in stored samples. So the one thing is because it's immunoglobulin based for the most part you know globulin based binding to troponin, you know this may be present in stored samples. So there's a publication just earlier this year where we looked at some patients in a clinical study. And we looked at measurements of times of troponin. So here we have two patients, patient one and patient two, and I just want to highlight the fact that here we see that the concentrations you know, bolded when they're above 99th percentile. And just for illustrative purposes, I use the overall 99th percentile for these analysis. So both patient one and patient two have concentrations above 99th percentile with troponin T for Abbot at the time on i1000 analyzer 2013 when we measured these samples. There was one that was above 68, quite high, 69. Interestingly when we actually measured the same samples on these patients with the Beckman assay, a regulatory approved assay in 2017, we actually obtained normal concentrations of a 4 and a 7 that was opposed to 68 with the Abbott assay, it was only seven. When we actually measured the Siemens ADVIA assay, we also had some elevations above the 99th percentile, but then when we measured the Ortho, which is the 3-site immunoassay, we also had low recovery of troponin, indicating that these results may be due to a macro. Importantly we then measured the same sample again on the Abbott. And now we have an elevation above 37, above 99th percentile on both patient one and patient two. And when we do a PEG precipitation, we actually get very low recovery. So these data illustrate that indeed macros even in clinicals, can exist for a long period of time or evidence stable and samples of the stored frozen so forth and undergo multiple freezing. So again, you know it's important laboratories are aware of this and have plans and procedures in place if confronted by clinicians that are questioning the pattern and elevations in certain patients with measuring high-sensitivity troponin assays.

这是一个真实的病例样本，但是在存存的样本中又如何呢？一方面是因为基于免疫球蛋白的球蛋白在大多数情况下都是结合肌钙蛋白的，这可能会出现在于储存的样品中。今年初就有发表，我们在临床研究中对一些患者进行了研究。我们研究了肌钙蛋白的测量的次数。这里有两名患者，患者一和患者而，我只想强调在这里我们看到超过 99 百分位数的浓度都以粗体显示。出于说明的目的，我将整体 99 百分位数用于这些分析。因此，当我们在雅培 i1000 分析仪 2013 上测量这些样品时，患者一和患者二的肌钙蛋白 T 浓度都高于 99 百分位数。有一个超过 68，非常高，69。有趣的是，当我们用贝克曼检测法，监管机构 2017 批准，对这些患者实际测量相同样品时，我们得到了 4 和 7 的正常浓度，而雅培测定是 68，它只有 7。当我们实际测量西门子 ADVIA 检测时，我们还有些升高超过了 99 百分位数以上，但是当我们测量奥森多时，3 位免疫测定，肌钙蛋白的回收率也较低，表明这些结果可能是由于一个大复合物。重要的是，我们再次在雅培上测量了相同的样品。现在，我们患者 1 和患者 2 的升高到了 37 以上，超过 99 百分位数。当我们进行 PEG 沉淀时，实际上回收率很低。因此，这些数据表明，即使在临床中，大复合物实际上也可以存在很长一段时间，或者可以在所存储的经过多次冷冻的冷冻样品中稳定存在。再次重申，重要的是实验室要意识到这一点，如果临床医生对某些患者模式和升高提出质疑，实验室应有计划和流程。

So it's important to know and it's important to interpret this information. It may well be because many of the studies that have been done on high-sensitivity assays, there are some done in real time, but a lot of them are done in frozen samples. So here's an example of a patient that was adjudicated as an MI but missed by a high-sensitivity assay, the 0/1 algorithm. So when you actually look at this patient, it was adjudicated to have an MI because the troponin which was done by contemporary assay were high, 85 at presentation and then it fell to 79 eighteen hours later. So clinically during the study and adjudication, they determined that was enough to say there was acute myocardial infarction. But when you look at this individual and you look at the troponin level that have been provided. You can see that troponin T starts off 8 and stays at 7 7 7. So the results are quite low and they're all normal with this patient. When you actually look at another high-sensitivity troponin assay, you are also getting very low concentrations well below 99th percentile. And even with the Abbott high-sensitivity assay, you know if you use the sex-specific cutoff this would be high. But one could question whether or not there's really changes in these concentrations at all. So again obviously the suggestive cause, there's been no macros measured in this patient. But I think it's important that you know we think about why one assay works and one another assay doesn't work. Obviously all assays work. When there's differences in interpretation whether or not they're missing clinical events versus not missing clinical events, I think we need to be mindful of this. Is there perhaps other factors at play analytically that may have caused this differences in assay performance.

所以了解这一信息很重要，而且解读这些信息也很重要。可能是因为在许多针对高灵敏度测定的研究中，有实时进行的，但其中许多是在冷冻样品中进行的。这里有一个示例，该患者被判为 MI，但被高灵敏度检测，0/1 法给错过了。因此当你实际查看该患者时，它被判为 MI，因为通过传统检测完成的肌钙蛋白水平很高，在就诊时为 85，然后在 18 小时后降至 79。因此在研究和判定过程中，他们决定这足以判断有急性心肌梗死。但是当你查看此人并查看所提供的肌钙蛋白水平时。你会看到肌钙蛋白 T 从 8 开始并停留在 7 7 7。因此结果很低，对于该患者来说一切正常。当你实际查看另一种高灵敏度肌钙蛋白测定法时，你也会得到非常低的浓度，远低于 99 百分位数。即使使用雅培高灵敏度测定法，你也知道如果使用特定性别的临界值，那会很高。但是人们可能会质疑这些浓度是否真的发生了变化。因此显然又是提示性原因，该患者没有测量到大复合物。但是我认为重要的是，你必须知道我们考虑为什么一项检测有效而另一项检测无效的原因。显然，所有测定都有效。当在解释是否遗漏临床事件与没有遗漏临床事件方面的解读存在差异时，我认为我们需要牢记这一点。在分析上是否可能还有其他因素在起作用，这些因素可能导致了测定性能的差异。

With all that being said, what is the clinical utility or safety of using the ESC 0/1 algorithm. So here's a systematic review that was just published journal heart. Here are different high-sensitivity troponin assays, obviously by different studies. And here is the four spots and they basically look at the sensitivity. So there are two metrics that people look at when regarding whether it's safe to rule out is sensitivity and negative predictive value. For sensitivity, most of emergency physicians have recommended the sensitivity needs to be 99% or higher in order to safely rule out. So as you can see here with these assays and these publications, the sensitivity approaches to 99th percentile. It's not quite there, 99% or 99th percentile. It’s close to

the 99th percent so the authors say that you know look at this meta-analysis, various different studies, the results support the use of 0/1 algorithm. However the algorithm may not be sufficiently safe if 1% miss-rate for myocardial infarction is desired. So again, there's little caveat there so there will be differences and clinicians will interprete these data differently. So sensitivity is what one metric is used. The other metric used is negative predictive value, and in that setting, some advoate negative predictive value greater than 99.5% is sufficient in order to rule out. So again something that needs to be discussed with clinicians where are these data, where is the performance and as a laboratory, if they are using this type of algorithms, clinical practice, you need to make sure that you have appropriate quality control procedures in place and quality assurance procedures and try to mitigate any inappropriate testing.

综上所述，用 ESC0/1 方法的临床实用性或安全性怎样？这是一篇刚刚发表在心脏期刊上的系统综述。这是不同的高敏感度肌钙蛋白测定，显然是通过不同的研究。这是四点，它们基本上是看灵敏度。因此，在确定是否可以安全排除时，人们会考虑两个指标：敏感度和阴性预测值。对于敏感性，大多数急诊医师建议敏感性必须为 99％或更高从而进行安全排除。因此如你在这些分析方法和出版物中所见，灵敏度接近 99 百分位数。还没完全达到，99％或 99 百分位数。它接近 99％，因此作者说这项荟萃分析，各种不同的研究，其结果支持使用 0/1 方法。但是，如果希望 1％的心肌梗死漏诊率，则该方法可能不够安全。同样这里没有什么需要注意的地方，因此会有差异，临床医生将以不同的方式解释这些数据。因此灵敏度是使用的一个指标。所使用的另一个标准是阴性预测值，在这种情况下，有人提倡阴性预测值高于 99.5％即足够进行排除。因此再次需要与临床医生讨论这些数据的位置，性能和实验室情况，如果他们使用的是这种类型的方法，临床实践，则需要确保已制定合适的质量控制程序和质量保证程序，并努力减小任何不合适的测试。

So as you may also recall, that’s to rule out. What about ruling in? So for the Abbott assay on the ESC guidelines, they say the change of between 0/1 hours of six or more is sufficient to rule in. So just want to highlight the fact that when we took the same sample, we measured eight times so same samples just measured eight times in different analyzers, we can see that the majority of them repeat exactly the same concentration. But we can see here that there are some you know repeats on measurements that exceed 6 ng/L. Just due to the variation of testing. So for example on this patient, average was 17 ng/L, the lowest one observed was 13, the greatest one observed was 20, this difference was seven. So kind of illustrate that even with high-sensitivity assay that are appropriately controlled, you can see this variation when the changes are just 6 ng/L or even lower at 4 ng/L which is illustrated here, using quality control material and measurements over twenty minutes, we see that there are drops in measurements. So again it may be difficult when using small changes to rule in for laboratories to be confident in the performance of their assays.

你可能还记得，这是为了排除。那么纳入呢？对于 ESC 指南中的雅培分析，他们说 0/1 小时之间改变为 6 或更多就足够进行纳入了。因此，我想强调一个事实，当我们采集相同的样品时，我们测量了八次，因此相同的样品只是在不同的分析仪中测量了八次，我们可以看到它们中的大多数重复完全相同的浓度。但是我们可以在这里看到一些重复测量值超过 6 ng/L。只是由于测试的变异。

所以举例，该患者的平均值为 17 ng/L，观察到的最低者为 13，观察到的最大者为 20，该差值为 7。说明即便使用适当控制的高灵敏度测定，当变化仅为 6 ng/L 或更低，在 4 ng/L 时，你可以看到这种变化，此处使用质量控制材料并测量二十分钟，我们看到测量值下降了。因此当用小的改变来纳入的时候可能会比较困难，可能很难使实验室对自己的测定方法充满信心。

So there are other algorithms besides 0/1 algorithm in order to use for high-sensitivity assay. There is 0/2 hour algorithm that has been developed obviously for both Roche and for high-sensitivity troponin I assays. This publication highlights the use of Beckman assay. There's also the High-STEACS pathway again demonstrated with the Abbott and with Siemens assay. And finally there are other approaches such as COMPASS-MI, which looks at two measurement changes between them and then this was published in the journal just last year and looked at both Abbott and Roche assays.

而除 0/1 方法外，还有其他方法可用于高灵敏度检测。对于罗氏和高敏感度肌钙蛋白 I 检测，显然已经开发了 0/2 小时方法。该出版物重点介绍了贝克曼检测法的使用。雅培和西门子检测再次展示了 High-STEACS 路径。最后还有其他方法，例如 COMPASS-MI，它查看它们之间的两次测量变化，然后在去年的杂志上发表了该方法，并研究了雅培和罗氏的检测方法。

So are there other algorithm that can be used? Yes there are other algorithms but all the other algorithms use some clinical information. So here is a nice publication from Louise Collins group in Australia, looking at various different clinical pathways. And so the one pathway that they look at in clinical pathways is no objective testing rule. And here you can see if you have two measurements below the overall 99th percentile in this case it's Beckman's assay. There is no ischemia on ECG, NOT score is zero and again in order to get that there is age and clinical information that is needed. But if that is employed, one can actually achieve a sensitivity greater than 99%. So again using clinical parameters, in addition to high-sensitivity assays and specific rules, one may be able to achieve sensitivity of both 99% which is illustrated in this nice publications from Australia.

那么还有其他可以使用的方法吗？是的，还有其他方法，但是所有其他方法都要使用一些临床信息。这是澳大利亚路易丝 柯林斯小组的很不错的发表，着眼于各种不同的临床路径。因此，他们在临床路径中研究的一种路径不是客观的测试规则。在这里你可以查看是否有两项测量值低于整体 99 百分位数，此病例中是贝克曼的检测方法。心电图上无缺血，NOT 得分为零，为了达到，有需要的年龄和临床信息。但是如果采用这种方式，则实际上可以实现大于 99％的灵敏度。再次使用临床参数，除了高灵敏度测定法和特定规则外，还可以达到 99％的灵敏度，这在澳大利亚的这本不错的出版物里有所说明。

What about just using two troponins? So this was a COMPASS-MI and the reason why it was called compass is the fact that different sites may achieve different types of performance and it's a little bit complicated. Let's walk over an example, so for

sites that were using an early protocol so the second sample collected anywhere from 45 minutes to 120 minutes or less in two hours. This is just an example for the Abbott assay. So if the presentation sample is less than six and the change between the baseline or zero hour and the next sample between 45 minutes to two hours, less than two hours if it was less than 4, so I get presentation 6 and then they change less than 4, one would be able to identify nearly 57% of the patients can be ruled out for MI. That's in this area right here, and here we're gonna have less than 0.2% of those individuals actually see have a thirty-day MI or death. So that's ruled out so you can see you nearly get up to 60% of patients by using this protocol. On the flip side, if someone came in with a troponin greater or equal to 30, with the a change greater or equal to 7, so higher than the 6. What we can be able to do here is the fact that we now we actually see 21% patients can be ruled out. So this type of approach, one can really serve to optimize based upon obviously clinical preferences and site preferences as to what sites believe are appropriate cutoff, they can monitor and measure those clinicians' regards to safety, negative predictive value, sensitivity. One can really optimize high-sensitivity troponin testing in the deltas in order to rule in and rule out individuals very promptly in emergency setting.

只使用两种肌钙蛋白又怎么样？这是 COMPASS-MI，之所以被称为罗盘（COMPASS），是因为不同的站点可能会获得不同类型的效果，并且有点复杂。让我们来过一个例子，对于使用早期方案的站点，第二个样本是在两个小时内从 45 分钟到 120 分钟或更短的时间内收集到的。这只是雅培分析的一个例子。因此，如果来院样本小于 6，并且基线或零小时与下一个样本之间在 45 分钟至 2 小时之间，不到 2 小时，改变如果小于 4，那么我得到的来院样本是 6，那么它们的变化小于 4，就可以确定将近 57％的患者可以排除 MI。就在这个区域，在这里，我们实际看到的 30 天 MI 或死亡人数中只有不到 0.2％。这个就排除了，因此你可以看到你几乎可以让 60%的患者使用此方案。另一方面，如果有人来，肌钙蛋白大于或等于 30，而改变大于或等于 7，则大于 6。我们在这里能够做的是，我们看到现在实际可以排除 21％的患者。因此，这种方法确实可以根据明显的临床偏好和位置偏好来确定哪些位置被认为是适当的临界值，从而进行优化，它们可以监控并测量那些临床医生对安全性，阴性预测值和敏感性的重视程度。可以真正优化高灵敏度肌钙蛋白测试，以便在紧急情况下非常迅速地纳入和排除个体。

So how about a one and done approach? So there may be some issues when looking at very low concentrations near the LoD and again analytically there's gonna be some variations but what about other a higher concentration. So here's a publication published in JAMA. At a 5 ng/L of concentration of high-sensitivity troponin I, for the Abbott assay, a lot of these cutoffs have been also at 5 ng/L, obviously used for other high-sensitivity troponin assays. And here you can see the negative predictive value, at some statistics, NPV is 99.5%. So regardless if you know that the MI was adjudicated based on the contemporary cardiac troponin or a cardiac troponin T or with a high-sensitivity assay. Your overall negative predictive value is of 99.5%. So at lease on that aspect, clinicians are comfortable on that metric. Maybe you find useful with this approach, less than five in order to rule out.

那么有没有一步到位的方法呢？当在 LoD 附近查看非常低的浓度时可能会出现一些问题，并且再次分析会出现一些变异，但其他较高的浓度又如何。这是在 JAMA 上发表的出版物。在高灵敏度肌钙蛋白 I 浓度为 5 ng/L 时，对于雅培分析，许多临界值也已在 5 ng/L，显然是用于其他高灵敏度肌钙蛋白的测定。在这里你可以看到阴性预测值，根据某些统计数据，NPV 为 99.5％。因此无论你是否知道 MI 是根据传统心肌肌钙蛋白或心肌肌钙蛋白 T 或使用高敏测定法来判定的，你的总体阴性预测值为 99.5％。因此至少从这方面来讲，临床医生对此指标很满意。也许你发现此方法很有用，用于排除的不到 5。

However if you use other common laboratory parameters, such as glucose, eGFR, in addition to a very low troponin measurement, one can see that here just by ruling in ruling out thirty day MI death over four thousand patients, what we observed is that you know we were close to 99% of NPC when using less than five. But some studies below that only 97%. However we add other parameters in here, we can increase sensitivity above 99th percentile. So there are perhaps ways that we can further improve the clinical sensitivity by incorporating: a. other laboratory variables or b. which was done demonstrated by Luise Colins group, use other clinical algorithms to optimize the performance to achieve both a high sensitivity and high NPV well above 99th percentile.

但是，如果你使用其他常规实验室参数，例如葡萄糖，eGFR，以及非常低的肌钙蛋白测量值，则可以看到，这里仅纳入或排除了 4000 例患者的 30 天 MI 死亡，我们观察到的是使用小于 5 时，我们就接近 NPC 的 99％。但是一些研究低于该值，只有 97％。但是，在此处增加其他参数后，我们可以将敏感性提高到 99％以上。因此，也许我们可以通过整合以下方法来进一步提高临床敏感性：a.其他实验室变量,或 b.这是由路易斯 柯林斯小组演示的，它使用其他临床方法来优化性能，以实现远高于 99 百分位数的高灵敏度和高 NPV。

So this leads to the last bit of talk in regarding a high-sensitivity testing patients with COVID-19. Again this is an emerging area, but it probably would be worthwhile to you know highlight a couple of studies recently published looking at this. And so the one large publication at China actually nicely demonstrated serial measurements of high-sensitivity troponin and patients that survived out of blue versus those who did not. So the one thing that's actually pretty noticable is the fact that patients that actually survived meeting concentrations for high-sensitivity were quite low and remained low, well below 5 ng/L. Of those that have bad outcome, you can start to see that the high-sensitivity troponin start to rise obviously, probably in conjunction with the worst clinical condition of that patient.

所以这带来了关于 COVID-19 患者的高灵敏度检测的最后一点介绍。这是一个新兴领域，但可能值得强调一下最近发表的有关此问题的一些研究。中国的一个重大发表实际上很好地展示了高敏感度肌钙蛋白的系列测量结果，以及意外存活的患者和未能存活的患者。实际上值得注意的一件事是，在达到高敏浓度的情况下存活的患者相当低，而且一只很低，远低于 5 ng/L。在那些结局不良

的患者中，你可以开始看到高敏感度肌钙蛋白开始明显升高，这可能与该患者临床状况极差有关。

So that was illustrated in one population. Another population when we looked at again patients that obviously unfortunately died versus recovered, if you look at the high-sensitivity cardiac troponin assay in this publication, we also see that the patients who did recover at presentation or admission, their high-sensitivity values are quite low at 3 whereas those who do not had very high troponin assay. So there's been a greater realization that especially with patients with COVID-19, their cardiac injury, cardiac dysfunction, heart failure among other things, cardiac injury and other aspects related to the heart are quite prevalent and is something of interest especially when assessing and interpreting these values.

这一点在一个人群中得到了说明。当我们再次观察另一个人群，不幸死亡对比康复的患者，如果你看到此出版物中的高敏感度心肌肌钙蛋白测定，我们还发现在就诊或入院时确实恢复的患者，其高敏感度值是相当低，是 3，而那些未能恢复的患者肌钙蛋白测定都高。因此有了一个更大的认识，特别是对于 COVID-19 患者，他们的心肌损伤，心脏功能障碍，心力衰竭，除了别的之外，心肌损伤以及与心脏有关的其他方面非常常见，尤其是在评估和解释数值时。

So one thing that is known so far and again with more details here. But if you look at this today with cardiac troponin and it's really important when consulted by clinicians, you know labs are familiar with what a high-sensitivity assay is versus not. They can inform the publication worth using a high-sensitivity assay versus not and what are the findings. And so definitely with cardiac troponin and many studies have suggested that obviously very high values, or values above 99th percentile are not very good for patient prognosis. And I think it's important to say that you know both contemporary assays and high-sensitivity assays are definitely appropriate for detecting mild cardio injury. However, data today may suggest that for other utility of high-sensitivity troponin testing because you may be able to detect low normal values, which actually indicate a favorable prognosis for the patient. And this is actually has been nicely illustrated by an opinion article by Nick Mills that his group talks about high-sensitivity cardiac troponin to be an ally in the fight against COVID-19 and this is really available and encourage those who are interested to read that and there are other publications are in the world that also discuss possible utility of high-sensitivity in the setting.

所以到目前为止，这一点有所了解，这里需要更多细节。但是，如果你今天用心肌肌钙蛋白来看这一点，而且在遇到临床医生咨询时就非常重要，实验室非常熟悉什么是高灵敏度测定法，哪些不是。他们可以通知出版方值得用高灵敏度的检测方法。对心肌肌钙蛋白的确如此，许多研究表明，非常高的值或高于 99 百分位数的值对患者的预后不是很好。我认为重要的是说，传统测定法和高灵敏度测定法都适合检测轻度心肌损伤。但是，今天的数据可能暗示了高灵敏度肌钙蛋白检测的其他用途，因为你可能能够检测到较低的正常值，这实际上表明患者的预后良好。尼克·米尔斯的一篇评论文章实际上很好地说明了这一点，

他的团队讲到高敏心肌肌钙蛋白是对抗 COVID-19 的盟友，并且确实存在，并鼓励那些有兴趣阅读的人。世界上还有其他出版物也讨论了高敏检测的用途。

So in summary I just want to illustrate, reiterate that detectable cardiac troponin support cost ratio and majority of the population is an alcohol marker vice finance a again when you are going in you using a high-sensitivity assay you need the right to see obviously need something around the normal and need something in the normal range in order to make sure you're monitoring assay appropriately. You want the right sample type, you don't want to accept different sample types during the course of, say, patient who is in the emergency department. You'll see variation. And most importantly you want the right lower limit, because if you're reporting inappropriate low end, clinicians may inappropriately discharge patients when in fact they may still have event occuring. Other things that are important, there are actually now performance goals, there's more commercial quality control that's available to monitor high-sensitivity sensitivity assays and there's a established error goal that allowable error can be used when measuring high-sensitivity assays. There are assay specific issues and so sites and laboratories need to be mindful of pre-analytical, analytical and post-analytical and local factors that may affect high-sensitivity interpretation. And lastly, probabaly can't state this or emphasize this enough, know your high-sensitivity assay, the one that you're running because all of them are a little bit different and the earlier testing protocols with stratification approaches that can be achieved with high-sensitivity troponin testing really need to be evaluated regarding to what is your assay, where's the evidence, where is the data in order to you know utilize that test for best patient care.

因此总而言之，我只想说明一下，可检测的心脏肌钙蛋白有利于成本比率，当你要用高灵敏度测定法进行分析时，你要明显看到正常范围，并且需要在正常范围内的东西以确保你能合适地监控分析。你想要正确的样本类型，你不想接收不同的样本类型，例如患者在急诊室期间。你会看到变化。最重要的是，你想要正确的下限，因为如果你报告的下限不当，则临床医生可能会让患者出院，这并不合适，而实际上他们仍然可能发生事件。其他重要的事情，实际上现在有了性能目标，还有更多的商用质控可用于监控高灵敏度的敏感性测定，并且有一个既定的误差目标，可以在测量高灵敏度测定时使用允许的误差。有分析特定的问题，因此现场和实验室需要注意可能影响高灵敏度解释的分析前，分析中和分析后以及局部的因素。最后，再次强调，要了解你正在运行的高灵敏度检测方法，因为所有检测方法都略有不同，并且可以通过高敏肌钙蛋白实现的使用分层方法的较早测试方案，确实需要对高敏肌钙蛋白测试进行评估，以了解你的检测方法，证据在哪里，数据在哪里，从而使用该检测方法为患者提供最佳照护。

So with that I'd like to thank you for listening, and I'll thank for all the collaborators and for funding I've received over the years and specifically from the Canadian's Institutes of Health Research, funded my working on cardiac troponin for last fifteen years and with that I'll end my presentation.

好的，讲到这里，我要感谢你们的聆听，也感谢所有合作者以及对我多年来的资助，特别是来自加拿大卫生研究院的资金，资助了我过去十五年心肌肌钙蛋白的研究，我就讲到这里。

Thank you Dr. Kavsak for sharing your wonderful presentation with us, we will now begin this Webinar's question and answer session.

谢谢你，卡夫萨克博士，感谢与我们分享你的精彩演讲，我们现在将开始本网络研讨会的问答环节。

First question is, can you share your thoughts on the evolution of the Beckman high-sensitivity troponin one assay?

第一个问题是，你能否分享对贝克曼高灵敏度肌钙蛋白检测发展的看法？

Yes, it's interesting because our first publication on high-sensitivity troponin reported I was in 2009 and that was on the prototype original Beckman high-sensitivity assay. So even with the prototype assay, when we measured material near 10 ng/L which again is the only material that can be, at that concentration we've measured with high-sensitivity assay. Even with the prototype assay, we achieved standard deviation of about 1 ng/L, so is less than 10% or about 10% at 10 ng/L. And you know what's surprising to me is that over you know the next twelve years or ten plus years, when we started measuring different versions of the high-sensitivity troponin assays. We've also always been able to obtain that very tight precision at the low end and that was illustrated in the latest high-sensitivity assays. And we're now we still are achieving standard deviations below 10 or less than 0.8. So that's one thing that's been very gratifying to see. Over the course of evolution, evolution and development of the high-sensitivity assays, the precision has always been there. Take precision down in the normal end. The other thing is it's been quite remarkable, as well as some of the aspects in regards to perhaps interferences or something that's would perhaps cause confusions because of high concentration, and for this I just want to highlight, perhaps the macros there definitely there's been some assays and we've definitely demonstrated this Beckman's assay that over the development of the high-sensitivity assays, some of these macro complexes are no longer detected with high-sensitivity, the latest regulatory approved high-sensitivity assays, which would be of huge benefit for patients coming in suspected with perhaps acute coronary event or they having an MI. You know, having an assay that's not perhaps impacted by macros could be very useful in this setting and so that's what one of the pleasant surprises over the years. Some of the interferences or some of the ways that assays have been redesigned don't detect macros the way they once did. I think it's also important to clarify the fact that we really don't know you know the clinical relevance of macro in this setting per se, so we need a lot more work kind of illustrated in the talk is that these could be confounding variables when patients come in with chest pain and you know they have an acute event, they have an elevation but it's really driving you know this really is the hallmarker, this really is the signal for an MI. But you know it may not be acute situation but we don't really know what is the long-term outcome on patients with

macro and so in the short-term setting you know not an assay that doesn't have an effect for the macro maybe a good thing. But we need to evaluate and do further follow-up studies regarding to what's the clinical relevance of macros.

是的，这很有趣，因为我们的第一个关于高灵敏度肌钙蛋白的出版物是我在2009年发表的，是在贝克曼高灵敏度测定的原型上做出来的。就算是使用原型检测，当我们测量材料接近到10 ng/L时，这也是唯一可以的一种材料，我们已经通过高灵敏度分析测量了该浓度。即使使用原型检测，我们也达到了约1 ng/L的标准差，因此在10 ng/L时小于10％或大概是10％。我感到惊讶的是，在接下来的十几年中，当我们开始测量不同版本的高灵敏度肌钙蛋白测定。我们也始终能够在低水平端获得非常窄的精度，这在最新的高灵敏度分析中得到了证明。现在，我们仍实现低于10或小于0.8的标准差。这是令人非常高兴看到的一件事。在高灵敏度测定法的发展，演变和发展过程中，始终保持着高精度。在正常情况下降低精度。另一件事是，它非常引人注目，还有一些方面，可能涉及干扰或由于高浓度而可能引起混乱，为此，我只想强调一点，也许大复合物肯定有，有一些检测，我们已经肯定地证明了贝克曼检测的重要性，即随着高灵敏度测定的发展，用高灵敏度检测其中的一些大复合物检测不到了，而最新监管机构批准的高灵敏度检测将具有巨大的优势，用于怀疑可能患有急性冠脉事件或有MI的患者。你知道，在这种情况下进行可能不受大复合物影响的检测会非常有用，这也是多年来令人惊喜的事情之一。重新设计检测方法的某些干扰或某些方法不再像之前那样检测大复合物。我认为澄清这一事实也很重要，我们本身并不真正了解这种情况下大复合物的临床相关性，因此我们需要在讨论中进行更多说明，这些工作可能会混淆变量。患者出现胸痛，你知道他们有急性事件，他们有升高，但这确实是标志，这确实是MI的信号。这也可能不是紧急情况，但是我们真的不知道大复合物患者的长期结局是什么，因此在短期情况下，大复合物没有影响的检测方法也许是一件好事。但是我们需要对大复合物的临床相关性进行评估并做进一步的后续研究。

Thank you. Next question is, can you elaborate on the analytical performance aspects related to Beckman’s assay.

谢谢。下一个问题是，你能否详细介绍与贝克曼分析有关的分析性能。

Yes, one thing to be confident that definitely is the fact that different versions of the Beckman’s assay over the past dozen years that I've looked at. From research to enhance versions, to the regulatory approved version, one is able to achieve excellent performance down low, very low lower limits of reporting a very good precision at normal concentrations. And that is definitely what's important, when we're looking at high-sensitivity assay that’s evident for Beckman. But you know make the statement, for all the high-sensitivity assays we're able to now achieve excellent performance of the low end with all high-sensitivity assays of the regulatory approved which is what is needed if clinicians are going to start use these values in order to make early decision-making in the ED.

是的，有一点可以肯定的事实是，我所观察的过去十年中贝克曼检验的不同版本。从研究到增强版本，再到监管部门批准版本，能在低浓度下获得出色的性能，而在标准浓度下，只需极低的下限即可报告非常好的精密度。重要的是，对于我们正在看的高灵敏度测定法时，贝克曼的显而易见。但是对于所有高灵敏度的测定，我们现在都可以通过监管部门批准的所有高灵敏度测定都能实现低端的出色性能，这是临床医生要开始使用这些数值时所需要的，以便在急诊做出早期决策。

Thank you next question, how robust are Beckman's 0/1 and0/2 algorithm?

谢谢你，下一个问题，贝克曼的 0/1 和 0/2 方法有多强？

I mean I don't have the opportunity to go through all the different algorithms and to see which ones are perhaps more robust or which ones may be more susceptible to analytical noise. Clinically they may work well, these publications say they work well. But in laboratory, you should be looking at your assays and seeing OK well how robust is the change criteria, how well they monitor the low cutoffs to do that and so. It's important to labs to look at that. So I talked briefly about Abbott, but there may be some performance issues that laboratories need to be aware of their you know utilizing say the Abbott assay for the 0/1 algorithm but they're all achievable if strict control that labs can do that. But you know there may be others, for example the Beckman assay using the 0/1 or 0/2 algorithms. You know the first 0/1 algorithm actually has changed less than 4, which is very similar to what we've seen with the COMPASS-MI having a change less than 4 for early rule out. So again a change less than 4, that again is something that should be especially lower concentrations below 10. You know a difference of 4 is really a different, is not due to analytical variation or a minor bias, it's probably due to patient or you know having more troponin in there just because it's typically upside of our analytical performance goal. So again you know with a COMPASS-MI, we see a change less than 4 and even with Beckman's 0/1 hour algorithm, obviously change less than 4. So that type of metric at the low end is something that is you know, probably some labs can monitor and feel comfortable to say that I can measure accurately I know what a change of 4, below 10 or what have you, is probably something different. And again typically what's also occurred, is that as you go from the 0/1 to 0/2 or 0/3 typically the delta increases. So a if you're good with 0/1 with the change of 4, two hours usually a higher delta and they should be definitely greater than the analytical variation. And that's also observed with for example a Beckman 0/2 assay, a 0/2 hour algorithm, the change there's less than 5. So you know the difference is less than 5, you can also at the low end. So again those types of algorithms where you're able to monitor if you're comfortable, may you know be abused and may allow labs to feel comfortable and report some of these assays. If clinicians are using them in that manner.

我的意思是我没有机会把所有不同的方法都过一遍来看看哪些方法可能更有力，或者哪些方法更容易受到分析噪声的影响。从临床上看，它们可能效果良好，这些出版物也说它们效果良好。但是在实验室中，你应该查看自己的检测方法，并看看改变标准有多强，他们对低临界值进行监测的能力等等。对于实验室而

言，这一点很重要。因此，我简短地谈到了雅培，但是实验室可能需要注意一些性能问题，例如使用 0/1 方法的雅培检测方法，但是如果实验室可以做到严格控制的话，这些都是可以实现的。但可能还有其他情况，例如使用 0/1 或 0/2 方法的贝克曼检测。第一个 0/1 方法实际上已更改为小于 4，这与我们所看到的 COMPASS-MI 更改为小于 4 以便提前排除的设定非常相似。变化小于 4，则较低浓度小于 10。你知道 4 的差异实际上是不同的，不是由于分析差异或较小的偏差所致，可能是由于患者或肌钙蛋白含量较高，因为这通常是我们分析性能目标的优势。COMPASS-MI 的变化小于 4，甚至使用贝克曼的 0/1 小时方法，变化也明显小于 4。因此，这种低水平指标的类型，也许有些实验室可以监控并轻松地说我可以准确地进行测量，我知道 4 以下的变化或 10 以下的变化可能有所不同。同样，通常情况是，当你从 0/1 变为 0/2 或 0/3 时，变化量通常会增加。因此，如果你对 0/1 的变化为 4 表示满意，则通常两个小时的变量会更高，并且绝对应超过分析变异。例如使用贝克曼 0/2 小时方法，也可以观察到这种情况，变化小于 5。差异小于 5，也可以在低水平端。你可以再次监控那些类型的方法，可能被滥用，并且可以让实验室感到自在并报告其中一些检测方法。如果临床医生以这种方式来用它们的话。

Wonderful, next question is can you discuss the impact of sample types and does China allow more than one sample type for the assay?

很精彩，下一个问题是，你能否探讨样品类型的影响？中国是否允许一种以上的样品类型用于分析？

You don't want to make different sample types when patients coming in you want to make sure the same sample type is used for measurement of troponin and high-sensitivity troponin. So you don't add other variability because we are looking at the small changes and so forth and low, evan at the higher end. So you want to mitigate that by just looking at one sample type. So typically that's what should be done. Now part of your investigations, if someone if a clinician’s questions that there may be something that's not making sense itself so important labs will have to look at different sample types and so not necessarily you want to report this to clinicians but part of your internal investigations is someone is saying I have an elevation that doesn't make sense. Sometimes what you'll see is that measurement in different sample types may be useful in order to identify if there's an interference that was elective contributed to that discrepant results. And so the ability to measure high-sensitivity troponin in more than one sample type is important for the lab so that they can, you know, perform additional testing if they are getting calls or getting clinical inquiries regarding discrepant results due to clinical picture. And so that has been demonstrated as a benefit for many different high-sensitivity assays and we did publish a paper in the Clinical Chemistry Laboratory Medicine looking at the effect of matrix on Beckman and Abbott assays and how that can be useful in identifying discrepant results. So something labs, you know, don't want to accept all different sample types from patients that are coming in to their hospital with potential chest pain, only accept one for clinical reporting. But in the event that there's some sort of a clinical concern or questioning some of those results, lab should have a protocol in

place to start testing with different sample types on that patient so that on a patient with a clinical concern query came in. So you can start the process to see okay, you know, is there an interference. And sometimes the first step is just measuring these troponin in different sample types and if you see wildly discrepant results that may tell you that there's something that could be contributing to that discrepancy.

患者来的时候你不想要不同的样本类型，你想要确定使用相同的样本类型来测量肌钙蛋白和高敏肌钙蛋白。因此，你不用增加其他可变性，因为我们正在看较小的变化，以此类推，还有低水平的，甚至较高水平的。所以你只想减少到检查一种样本类型。通常就是应该这样做。现在，这是你研究的一部分，如果有人，如果临床医生提出疑问，就可能存在某些本身不合理的问题，实验室就要查看不同的样本类型，但也不一定要向临床医生报告，而是内部调查的一部分，可能有人在说我的升高解释不通。有时你会看到，对不同样本类型的测量可能会有用，用以确定是否存在选择性地导致差异结果的干扰。因此，能够在一种以上样品中测量高灵敏度肌钙蛋白的能力对实验室而言非常重要。所以，如果他们接到电话或因临床情况而导致对结果不符的临床询问，他们就可以进行其他测试。这也被证明对许多不同的高敏测定法都是有益的，我们确实在《临床化学实验室医学》上发表了一篇论文，研究了基质对贝克曼和雅培测定法的影响，以及该方法如何用于鉴定差异结果。实验室不希望接受来院有可能胸痛的患者的所有不同类型的样本，而只接受一种用于临床报告的样本。但是，如果存在某种临床问题或对其中一些结果提出疑问，实验室应该有一个方案，开始对该患者进行不同样本类型的测试以应对。你可以启动该流程以查看是否正常，知道是否存在干扰。有时，第一步只是测量不同样品类型中的这些肌钙蛋白，如果你发现不一致的结果，可能会告诉你导致差异的某些原因。

Wonderful last question is can you elaborate on macro complexes and how Beckman assay is less affected?

精彩，最后一个问题是，你能否详细说明大复合物，以及贝克曼检测如何不大受影响？

These have been documented in literature for a number of years. Even with contemporary assays, there has been some reports of macro complexes and so you know one of the caveats was you don’t know macro complex unless you start to do some investigations. And you never get alert to that typically in the lab unless clinicians start to, you know, do further investigations. They can't understand why there's an elevation. But in absence of all that someone comes in and again it's the acute coronary situation, acute cardiac injury using change and differences in concentrations of cardiac troponin that may be very useful as well and that you know the patient does have a macro, also looking at that change cause you know there maybe a macro, there's also other troponin that coming out from the heart and you'll start to see the rise and fall. So it's not the fact that you still so important that if you see an elevation, it's still important to do the serial testing to see if it 's if you know for some patients to see if it's increasing and decreasing. You know, and that may be useful in the acute situation and setting and those are some of the queries that we get

is that patients come in and get admitted and they do the workup and they go it seems like there's anything wrong with a heart and I can't see or understand why the troponin was elevated and so it's part of you know laboratories responsive work with clinicians to try to provide some solutions to their clinical dilemmas. So what it does appear in the evolution of high-sensitivity troponin testing, it does appear to be some complexes that architect will buy some assays versus others and and again it's really surprising, it was really nice to see from, you know, the prototype Beckman assay to the final version that some of these macro complexes went away. We weren't detecting them with a contemporary essay, with their high-sensitivity approved assay, we didn't see that. So that may be a benefit because you lose that confounding variables high troponin comes in you are not seeing these high troponin concentrations with some of the more with some high-sensitivity assays. So that could be a benefit. I still think we don't really understand why do some patients develop a macro complex with troponin, how long do they persist in patients of macro complex. Today you know because there's some antibody bound. Does that patient comes back to you years later they still have that or six months later they stop the macro in there. Why did they get that? Why is there immunoglobin and binding to troponin and causing those elevations and so forth? What's the mechanism behind that? And what's the long-term outcome? In the short term, it may be very important to say yeah you're not having acute event but in long term there's something needs to be followed up. So there's a lot of things we don't know about macros. But at the end of the day, it is an area that seems to be obviously something that seems to cause discrepancies between assays which we looked to a couple years ago but has been nicely demonstrated in the Clinical Chemistry publication by Lambing and colleagues in the March issue of this year. They really say that these macro could be main reason why we see discrepancies between the assays and so something that we need more work to try to understand for sure.

这些已经在文献中记录了很多年。即使采用传统检验方法，也有一些关于大复合物的报道，因此你要知道的一个警告是，除非你开始进行一些调查，否则你不会了解大复合物。而且，除非临床医生开始进行进一步的调查，否则你通常不会在实验室中意识到这一点。他们不明白为什么会有升高。但是在什么都没有的情况下，急性冠脉疾病，急性心肌损伤，使用心肌肌钙蛋白浓度变化和浓度差异可能非常有用，并且患者确实有大复合物，关注这种变化，可能有大复合物，还有其他从心脏出来的肌钙蛋白，你会看到上升和下降。如果你看到抬高的情况，那么进行系列检测以判断对于某些患者是在升高还是下降。这在紧急情况和环境中可能很有用，而我们所收到的一些疑问是，患者进来，收治入院，进行了检查，然后似乎心脏没什么问题，但我不明白为什么肌钙蛋白升高了。所以这是实验室与临床医生进行响应性工作的一部分，为他们的临床难题提供部分解决方案。它确实出现在高敏肌钙蛋白测试的发展过程中，它似乎确实是有些复合物，architect 会用一些检测方法而不是其他检测方法，这令人感到非常惊讶。很高兴看到从原型开始，到贝克曼检测的最终版本，某些大复合物没有了。我们并不是通过传统检验来检测它们，只是通过高敏检测方法，我们没有看到而已。这可能是一个优势，因为你丢掉了高敏肌钙蛋白的混杂变量，在某些高灵敏度测定中看不到了。这可能是个好处。我仍然认为我们并不真正理解为什么有些患者会出现肌钙蛋白的大复合物，有大复合物的患者又会持续多久？今天你知道是因为有一些抗体结合。几年后该患者会回来找你，那个还会有吗？还是六个月后，他们的大复合物就停止了。他们为什么会有？为什么

存在免疫球蛋白并与肌钙蛋白结合并引起这些升高？其背后的机制是什么？长期结果是什么？短期内对你说你没有急性事件，这可能很重要，但长远来看，有一些事情需要进行随访。我们对大复合物还是有很多不了解的地方。但归根结底，明显是这一领域导致了检测间存在差异，我们也研究了好几年，但 Lambing 及其同事在今年三月份的《临床化学》中的发表进行了很好的解释。他们说这些大复合物可能是我们看到检测方法之间的差异的主要原因，因此我们需要做更多的工作才能确定地理解这些问题。

Thank you very much for your insights, Dr Kavsak. This now concludes our question and answer session. I would like to once again thank Dr Peter Kavsak for providing his excellent presentation and thanks to all of you and the audience for watching this AACC Webinar, supported by Beckman Coulter China. If you have any questions following this program, please email our customer service, at custserv@aacc.org, again that's custserv@aacc.org. Thank you very much, and have a wonderful rest of the day.

卡夫萨克博士，非常感谢你的见解。现在我们的问答环节到此结束。我要再次感谢彼得 卡夫萨克博士的精彩演讲，并感谢大家和观众观看了由贝克曼库尔特中国支持的 AACC 网络研讨会。如果你对本项目有任何疑问，请给我们的客户服务发送电子邮件至 custserv@aacc.org，再说一遍是 custserv@aacc.org。非常感谢你，祝今天愉快。