UNITED STATES OF AMERICA
DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTERS FOR MEDICARE AND MEDICAID SERVICES
+ + + + +

MEDICARE EVIDENCE DEVELOPMENT & COVERAGE
ADVISORY COMMITTEE
+ + + + +
MEETING

+ + + + +

WEDNESDAY
NOVEMBER 9, 2011
+ + + + +

The Advisory Committee met in the Auditorium of 7500 Security Boulevard, Baltimore, Maryland, at 8:00 a.m., Clifford Goodman, Ph.D., Chairman, presiding.

PRESENT:

CLIFFORD GOODMAN, PhD, Chair
STEVE E. PHURROUGH, MD, MPA, Vice Chair
RENþ CABRAL-DANIELS, JD, MPH, Member
PETER HESELTINE, MD, Member
WARREN JANOWITZ, MD, JD, FACC, FAHA, Member
ROBERT MCDONOUGH, MD, JD, Member
RYAN H. SAADI, MD MPH, Member

DAVID J. SAMSON, MS, Member
ROBERT L. STEINBROOK, MD, Member
BRIAN SEAL, RPh, MBA, PhD, Industry Representative
YORAM RUDY, PhD, Guest Panel Member
JAMES ROLLINS, MD, CMS Liaison
MARIA ELLIS, Executive Secretary

LISA EGGLESTON, RN, MS, CMS

INVITED GUEST SPEAKERS

REMY R. COEYTAUX, MD, PhD, Duke Clinical Research Institute

JEROME L. FLEG, MD, National Heart, Lung, and Blood Institute, NIH

PHILIP LEISY, BS, MD Candidate, ECU Brody School of Medicine

ROB MACLEOD, PhD, University of Utah

SCHEDULED PUBLIC SPEAKERS

AMIR BEKER, PHD, Chairman, BSP Biological Signal Processing, Inc.

MICHAEL IMHOFF, MD, PhD, Ruhr-University Bochum, Germany

JOSEPH T. SHEN, MD, MCG Technology Developer, Founder and Managing Member, Premier Heart, LLC

JOHN E. STROBECK, MD, PhD, Heart-Lung Associates, PC

C-O-N-T-E-N-T-S

P-R-O-C-E-E-D-I-N-G-S

8:03 a.m.

MS. ELLIS: Good morning. And welcome Committee Chairperson, Vice Chairperson, members and guests. I am Maria Ellis, the executive secretary for the Medicare Evidence Development and Coverage Advisory Committee, MEDCAC.

The Committee is here today to discuss the evidence, hear presentations and public comment and make recommendations concerning the currently available evidence regarding the use of electrocardiogram (ECG)-based signal analysis technologies to detect myocardial ischemia or coronary artery disease.

The following announcement addresses conflict of interest issues associated with this meeting and is made part of the record. The conflict of interest statutes prohibit special government employees from participating in meetings that could

affect their, or their employer's, financial interests.

Each member will be asked to discuss any financial conflicts of interest during their introduction. We ask, in the interest of fairness, that all persons making statements or presentations disclose if you, or any member of your immediate family, own stock or have another formal financial interest in any company, internet or e-Commerce organizations that develops, manufactures, distributes and/or markets electrocardiogram-based signal analysis technologies.

This includes direct financial investments, consulting fees and significant institutional support. If you haven't already received a disclosure statement, they are available on the table outside of this room.

We ask that all presenters please adhere to their time limits. We have numerous presenters to hear from today and a very tight

agenda. And, therefore, cannot allow extra time. There is a timer at the podium that you should follow. The light will begin flashing when there are two minutes remaining and then turn red when your time is up.

Please note that there is a chair for the next speaker, and please proceed to that chair when it is your turn. We ask that all speakers addressing the panel please speak directly into the mic and state your name.

For the record, voting members present for today's meeting are, Dr. Steve Phurrough, Dr. Rene Cabral-Daniels, Dr. Peter Heseltine, Dr. Warren Janowitz, Dr. Robert McDonough, Dr. Ryan Saadi, David Samson and Dr. Robert Steinbrook.

A quorum is present and noone has been recused because of conflicts of interest. The entire panel, including non-voting members, will participate in the voting. The voting scores will be available on our website following the meeting. Two averages will

calculated. One for voting members and one for the entire panel. I ask that all panel members please speak directly into the mics. And you may have to move the mics, as we may have to share.

This meeting is being webcast via CMS in addition to the transcriptionist. By your attendance you are giving consent to the use and distribution of your name, likeness and voice during the meeting. You are also giving consent to the use and distribution of any personally identifiable information that you or others may disclose about you during today's meeting. Please do not disclose personal health information.

If you require a taxi cab, there are telephone numbers to local cab companies at the desk outside of the auditorium. Please remember to discard your trash in the trash cans located outside of this room.

And lastly, all CMS guests attending today's MEDCAC meeting are only

permitted in the following areas of CMS single site. The main lobby, the auditorium, the lower level lobby and the cafeteria. Any persons found in any area other than those mentioned will be asked to leave the conference and will not be allowed back on CMS property again.

And now I would like to turn the meeting over to Dr. James Rollins.

DR. ROLLINS: Good morning. My name is Jim Rollins and I am the director of the Division of Items and Devices in the Coverage Analysis group here at CMS. MEDCAC served three main purposes for CMS.

Number one, to get input from experts in the field on the topic, and that information helps us to strategize our efforts related to future activities on that particular topic.

Number two, to help disseminate information to the general public. And, number three, a more immediate use of

MEDCAC's, along with external technology assessments, is to help us craft national coverage determinations.

I would like to thank the members of the MEDCAC Committee, especially the Chairperson, as well at the Vice Chairperson for leading and participating in this morning's discussion.

DR. GOODMAN: Thank you, Dr. Rollins. We have just this day for a full agenda on a topic with considerable potential impact on the wellbeing of Medicare beneficiaries and with that in mind we expect that all of our guests, those providing scheduled public comments, and any who may provide open public comments, as well as my fellow MEDCAC members, will be on point and concise today.

And when it is your turn to speak please speak into the microphone. If you don't do that we won't hear you and our trusty court reporter won't hear you either, which

means that the important things that you have to say won't get into the record. And I'd trust that you'd like to have them in the record.

We have today a time for scheduled public presentations. I understand that there will be four such presentations, each of which has been allotted a maximum of seven minutes. So for each of those four presentations that are scheduled, seven minutes.

Because of our tight agenda today, including the need to hear from all of our speakers and to provide for full discussion and consideration by this committee, we will need to adhere to those seven minute limits.

Later we'll hear from any open public comments, each of which would be allocated one minute. We kindly, though firmly, suggest that each scheduled speaker and each public commenter think now, think now about focusing your presentations on information that pertains to directly to

today's voting questions.

If you plan to present material that you soon find would be repetitive of a previous speaker, or that is merely background information about the organization that you represent, you might consider dispensing with that material and focusing instead on what you want this committee to know about the questions before us today. In any case, please do heed the traffic light system. Do know that we will proceed to the next speaker once you have used your allotted minutes. Thanks very much on that.

Please also silence your cell phones at this time, and any other communications gizmos that you might be carrying with you.

Note that all speakers will have to sign a disclosure form, so if you aren't on a list yet to speak and you're going to be an open, public speaker and haven't made out one of those forms for Ms. Ellis, please make sure

you do that.

Now we'll move to disclosures, I'll start. And I apologize, mine tends to be a little long. I'm Cliff Goodman, a Senior Vice President of the Lewin Group. Lewin is one of multiple subsidiaries of OptumInsight, which is a health care information and analysis firm.

OptumInsight, in turn, is one of multiple subsidiaries of United Health Group. On behalf of the Lewin Group I work on projects for a range of government agencies and private sector organizations in the U.S. and abroad, including pharmaceutical biotechnology and medical device firms large and small. I have no interest to declare pertaining to today's topic.

Dr. Phurrough.

DR. PHURROUGH: I'm Steve Phurrough and I have no financial conflicts of interest.

MS. CABRAL-DANIELS: Rene Cabral-

Daniels, I likewise, have no conflict of interest.

DR. HESELTINE: I'm Peter Heseltine, I have no conflicts of interest.

DR. JANOWITZ: Warren Janowitz, no conflicts of interest.

DR. MCDONOUGH: Bob McDonough, no conflicts of interest.

DR. SAADI: Ryan Saadi, no conflicts of interest.

MR. SAMSON: David Samson, no conflicts of interest.

DR. STEINBROOK: Robert Steinbrook, no conflicts of interest.

DR. SEAL: Brian Seal, no conflicts of interest.

DR. RUDY: I'm Yoram Rudy, and I am on the Scientific Advisory Board and hold equity in CardioInsight Technologies.

DR. GOODMAN: Thank you all. And thank you for your disclosures. By the way, if during the course of the day, panel, it

should occur to you that a conflict might arise that you had not realized earlier we can enter it into the record at that point. Just a little reminder there.

I believe now we're going to move to the CMS presentation and voting questions, correct?

MS. ELLIS: Yes.

DR. GOODMAN: And that will be Lisa Eggleston. Thank you, Ms. Eggleston.

MS. EGGLESTON: Good morning. And welcome again to CMS's MEDCAC on the use of ECG-based signal analysis technologies to detect myocardial ischemia or coronary artery disease.

The purpose of my remarks is to provide a brief background for the MEDCAC voting questions, and to read the questions. As you see on the slide the questions below refer to the use of electrocardiogram, you'll hear it referred as ECG, -based signal analysis technologies, SAECG, you will hear me

refer to it from now on, used for the purpose of detecting coronary artery disease, or CAD, in patients who are asymptomatic, but have increased risk factors for CAD or in patients who present with signs or symptoms suggestive of acute coronary syndrome, ACS, with or without chest pain and who are not triaged for emergent reperfusion therapy.

Furthermore, for the purposes of this meeting, SAECG technologies are defined as those that, assess electrical activity of the heart and transform and/or interpret the signal through spatial imaging or advanced mathematical modeling to produce new indices and are commercially available in the United States. This does not include the standard 12-lead ECG or other technologies used only to diagnose arrhythmias.

Health outcomes of greatest interest for this MEDCAC include mortality, myocardial infarction, cardiac function and quality of life.

For the voting questions the following scale will be used to identify the level of confidence with one being the lowest, or no confidence, and five representing a high level of confidence. Also for purposes of this MEDCAC, the terms ECG-based signal analysis technologies and SAECG technologies will be used interchangeably. And as you see on the slide there are the scores from one through five.

MEDCAC question Number 1: How confident are you that there is adequate evidence to determine whether or not SAECG technologies are able to reliably and accurately detect coronary artery disease in asymptomatic patients at risk for the disease or patients with signs and symptoms suggestive of ACS with or without chest pain?

If the result of Question 1 is at least intermediate with a mean vote greater than or equal to 2.5 in any of the conditions noted how confident are you that ECG-based

signal analysis technologies are able to reliably and accurately detect coronary artery disease in asymptomatic patients at risk for the disease, or patients with signs and symptoms suggestive of ACS with or without chest pain. If the result of Question 2 is at least intermediate, again with the mean vote great than or equal to 2.5 in either of the conditions noted, continue on to the following questions for the specified disease process.

Number 3: How confident are you that there is adequate evidence to determine whether or not the incremental information obtained from SAECG technologies, beyond that provided by the standard 12-lead ECG, improves physician decisionmaking in the management of, coronary artery disease in asymptomatic patients at risk for the disease or in patients with signs and symptoms suggestive of ACS with or without chest pain?

Number 4: If the result of Question 3 is at least intermediate, again

with a mean vote greater than or equal to 2.5, how confident are you that the incremental information obtained from SAECG technologies, beyond that provided by the standard 12-lead ECG, improves physician decision making in the management of, coronary artery disease in asymptomatic patients at risk for the disease and patients with signs or symptoms suggestive of ACS with or without chest pain?

Number 5: How confident are you that there is adequate evidence to determine whether or not the incremental information obtained from SAECG technologies, beyond that provided by the standard 12-lead ECG, can eliminate the need at the level of an individual patient, for diagnostic laboratory testing, for example troponin, non-invasive tests of cardiac anatomy or functioning, for example stress testing or echocardiography, et cetera or invasive testing of cardiac anatomy, functioning, for example coronary angiography?

Number 6: If the result of

Question 5 is at least intermediate, with a mean vote great than or equal to 2.5, how confident are you that the incremental information obtained from SAECG technologies, beyond that provided by the standard 12-lead ECG, can eliminate the need at the level of an individual patient for diagnostic laboratory testing, non-invasive tests of cardiac anatomy functioning, for example again, stress testing or echocardiography, et cetera, and invasive testing of cardiac anatomy or functioning, for example coronary angiography?

Number 7: How confident are you that there is adequate evidence to determine whether or not the use of SAECG technologies significantly improves patient health outcomes?

Number 8: If the result of Question 7 is at least intermediate, with a mean vote greater than or equal to 2.5, how confident are you that the use of SAECG technologies significantly improves patient

health outcomes?

Number 9: What evidence gaps exist in the field of signal analysis ECG devices?

And Number 10: How confident are you that these conclusions are generalizable to the Medicare patient population and to community-based settings?

Our contact information, myself, Lisa Eggleston and Dr. Susan Miller who is the medical officer for this MEDCAC. Thank you.

DR. GOODMAN: Thank you very much, Ms. Eggleston, well stated. Before we proceed to the next speaker I just want to clarify for panel, and for other participants today, that that long list of ten questions really can be broken down into a more straightforward set.

Basically, it's four pairs of voting questions. It's four pairs of voting questions. Each pair does the following two things, the first of the pair asks about the adequacy of the evidence. Not what the evidence says but the adequacy of the evidence

to draw any findings.

The second of each pair asks if the evidence is adequate, what is it saying? Now the four pairs ask for a series of things. The first pair is about detection. The second one is about physician decision making. The third pair is about the ability to eliminate the need for certain other tests, that is kind of substitutability. And the fourth pair is about improvement of patient outcomes.

So what we're about today is detection, impact on physician decisionmaking, eliminating the need for certain alternative tests. And the improvement of patient outcomes. Those are the four pairs of voting questions. After the four pairs of voting questions there are two non-voting questions, both of which are equally important. And that's Question 9, which is about any evidence gaps. By the time we get to Question 9 we may have realized that there's some evidence that needs to be generated to fill in some gaps.

And the final question, Question 10, is about generalizability or external validity. And this is always a question that the MEDCAC addresses. And they deal with whether or not the findings to that point are applicable in community settings and are applicable to Medicare beneficiaries.

So it sounds like kind of a complicated set of ten questions, and not to minimize any of those, but they are structured in a pretty forward way. Okay? Very good.

We'll move now to our first invited speaker. And this is Dr. Rob MacLeod. He's the Associate Professor of Bioengineering and Internal Medicine at the University of Utah Scientific Computing and Imaging Institute.

Dr. MacLeod, you're scheduled for about 40 minutes it looks like and less than that is acceptable as well. And we welcome you and look forward to your comments and wish we were there.

DR. MACLEOD: Thank you, this photo was to inspire you to come and visit Utah. In a couple of weeks from now it'll start to look like this.

This is the actual topic I want to talk to you about today. To start out with I have to say when Susan first approached me and called me many times before she finally managed to reach me to ask me to come and present to you I had no idea you even existed. I had no imagination for what this session was going to be and what sort of information I could help you come up with and provide for you. And through many phone calls Susan was terrifically helpful. And hopefully I've got a collection of information, a collection of insights that I can share with you, and happy to share with you to help you in your decisionmaking today.

DR. GOODMAN: Dr. MacLeod, if you could just pause for a moment. Court reporter, is the lavalier insufficient? And

would you want him to switch to the podium mic? What do you need to hear him?

(Off microphone discussion.)

DR. GOODMAN: Behind the podium? But he's using a lav. Is that okay?

COURT REPORTER: That's fine.

DR. GOODMAN: Do we need to turn up the volume on the lavalier? Okay. Please proceed, Dr. MacLeod, sorry for the interruption.

DR. MACLEOD: Okay. No problem at all. As I was saying, so I tried to adopt this presentation to, hopefully, your needs.

And I hope you will feel free, especially the Committee, to interrupt me and ask me questions if they're relevant points that you want more depth on, and to scoot me along if I'm covering material you've heard before and don't need to hear again.

DR. GOODMAN: Yes, Dr. MacLeod, what we'll probably do is hear you out and then we'll go to questions. And we'll take

notes during your talk if we need to ask questions.

DR. MACLEOD: That's fine too absolutely.

DR. GOODMAN: Go ahead.

DR. MACLEOD: Thank you very much. My background is in physics, electrical engineering, physiology and biophysics. I have degrees in all three areas. That's the way you used to have to become a biomedical engineer. And so I bring that multifaceted approach to this problem. And it's a problem or question I've been involved with off and on for over 30 years.

And almost that long I've had the pleasure of knowing Dr. Yoram Rudy, who's your guest panelist today. And I will certainly encourage you to take close note of his comments. He has additional deep expertise in this area. And so things that I may not be able to cover he certainly can.

I want to tell this story really

in three parts. And the first part has to do with the information source for any ECG-based analysis and the question of whether there's additional information available to further enrich and enhance and improve the diagnostic capability of this general technique of electrically-based identification of myocardial ischemia and coronary artery disease.

And so I'll spend some time talking about that. Then I want to tell you about what it is that specifically the inverse problem, and this is where it's going to get a little technical and I'll do my best to get you through this. What the inverse problem and the additional information that we use for a modern world, this notion of signal analysis, additional information -- the sort of theoretical underpinnings and the practical application of those theories to further enhance information we're able to extract from that raw data, from the ECGs we get from the

body surface. So that's the inverse solution part.

And then I want to share with you some of the, sort of modern results, you know, where are we today as I see it in this domain. Again a field that's been around for a long time.

And I want to start by saying that this technique can work. This is an example I'm going to show you. I'm going to play a movie here. And on the left-hand side you'll see a body surface potential map. Here you have electricity, voltage, encoded as color. This is ECG recorded with higher resolution that you typically have with a standard 12-lead ECG. On the right-hand side you see the same sort of layout.

This is the recording from the body surface of a patient, at rest, not showing any signs of myocardial stress. Down below here you see a smaller rendering of the surface of the heart. The red lines there are

meant to indicate the coronary arteries, for reference, give you some spatial orientation. And on the right-hand side we have data from the same patient recorded during a very specific situation that induces ischemia in a very transient way. And that's during a procedure called angioplasty, this is when a balloon is inflated into a partially occluded coronary artery. That blocks the flow of blood, mimics the situation very early in a heart attack, in myocardial infarction. And produces myocardial ischemia.

And so we're going to compare, in this movie I'll show you, what the body surface potentials look like. Both before and during this episode of induced ischemia. And also what the epicardial, or cardiac surface potentials, look like at the same time. And we'll just sort of walk through this movie and you'll see a whole heartbeat play out.

And you're going to see the beginning of the heartbeat, you see things

look very similar here. Later in the heartbeat you see some dramatic differences in the body surface maps of the patient during ischemia. You see those differences reflected on the heart surface as well. So we're able to predict this, this is not measured. These are measured.

The inverse solution allows us to go from that measured information on the body surface non-invasively, non-painfully acquired, to the invasive information on the heart surface.

And this technique can work. There are many examples of the applications of this technique to other disciplines in cardiac pathophysiology. This is one relevant I think to our discussion today. These results are 20 years old. This is not new. So this technique has been around for awhile, the idea has been around for awhile. A lot of the underpinnings have been around for awhile.

It doesn't always work quite this

well. And that's what I want to get to, certainly, towards the end of the talk, is why I don't think it works as well as it might.

The motivation for this whole approach should be fairly clear to you especially, mostly you physicians, in a couple of different scenarios, that of ischemia monitoring, the patient who has come into the emergency room with symptoms, signs of a heart attack, is placed on an ECG and the ECG is recorded in a continuous manner in order to determine whether or not that patient is having a full-blown myocardial infarction and how that infarction is progressing or potentially how the cures, the interventions for that infarction, are actually resolving the disease.

And we know, however, that the error rates are extraordinarily high. Depending on the literature you look at 30 to 50 percent is the error rate, in both directions, of misdiagnosing patients with

apparent myocardial ischemias when they enter the emergency room. So we have a major problem that should be a concern, I think, to everybody. These are error rates we really, as patients even, shouldn't be happy with.

In the other setting of a stress test the conditions that we take patients to when there are signs of coronary artery disease, when there is suspicion of underlying consequences of that coronary artery disease. Even there the sensitivity and specificity of this particular test is very low.

And the question now becomes what additional methods/approaches can be brought to bear to use what is easily available information, very cheaply and painlessly available, non-invasive information, and to extract enough useful diagnostics out of that information in order to improve these numbers and really fulfill the potential of this general approach?

So that's really about the

background. Now sort of the Part 1, the body surface potentials. The information, the raw information. So a 12-lead ECG is the standard of care. Obviously all these techniques are based on additional information, additional channels of signal. And so we transform from the ECG, here you see on the left, the typical picture of the ECG and its various projections, to the earliest recordings, or earliest publications of body surface potential mapping going back to the early 60s, by a colleague of mine, Bruno Taccardi. And some of the more modern technology that replaces what was a very tedious process, as you can imagine, in 1960. Recording multiple sites on the body surface, fronts and back of the body surface.

With this change in technologies from a small number of electrodes to many, many electrodes we also transform our picture of the underlying source of these activities. And I'll come back to sources again, this is

a key part of this whole story. We go from an implicit notion of what's called a dipole. A very simple source that consists of a source in a sync, current leaving, current entering. Closely spaced points, that produces a physical current dipole. The physics of it are well known. It's a gross approximation of the electrical activity of the heart and it's the basis for standard electrocardiography. It's the basis for diagnosis and interpretation of the ECG.

As we move toward a more spatial sampling at higher resolution with more electrodes we move toward more complex underlying source models. The source now becomes not just something that can be encapsulated in a single quantity as simple as the dipole to something that we call mapping, that somehow has spatial distribution, that defines in space and time the electrical activity coming from the heart.

And that's what body surface

potential mapping provides. That's what any additional electrodes on the body surface provides, is this transition from a simple model to a more complex model. And with that additional complexity comes cost, there's no question. But also comes the potential for useful diagnosis.

The performance of the standard ECG is very poor. I've shown you the overall statistics. Here's a paper I happened to come across in preparation for this talk. A very recent paper from the American Journal of Cardiology, just this year. This shows the sensitivity and specificity of the ability to differentiate ST-segment elevation myocardial infarction from non-ischemic ST elevation.

So identifying which patients are actually having ischemia from those who are not when their ST-segments, which is the feature of the ECG use for diagnosis are abnormal. And the graphs you see there, the bars you see there, are the performance of

sensitivity and specificity of seven experienced experts in a state-of-the-art clinical emergency room. People who are used to looking at this everyday, day in, day out.

And what you see here is, first of all, fairly low numbers overall. Sensitivities don't get much higher than the low 80s. Specificity is a little bit, in one case, a little higher than the mid-80s. So those numbers are, again, in line with what I showed you before.

But what you also see that's significant here is the variation in observers. Each one of these bars corresponds to one physician. And there's a dramatic difference. Between a 55 percent sensitivity and an 83 percent sensitivity across experienced observers. So the ECG as we're using it today is not a useful tool, it's a very blunt instrument, which is of course what motivates these additional more costly, more invasive, substantially more painful

procedures on patients.

So the question is does more leads, does more information, more electrocardiographic source information buy us more diagnostic power? And there's lots and lots of papers you can look through in the literature that certainly, in small samples, in animal preparations, in small samples of human studies indicate that more information can buy you more background, more insight.

The mechanisms of things like the spatial distribution of QT interval, that's another parameter that we use to characterize features of the heart, are available through body surface type mapping.

Body surface potential mapping during Percutaneous Transluminal Coronary Angioplasty. That's actually the situation I showed you in that video at the beginning. So this is using body surface mapping during angioplasty to indicate regional myocardial conduction delays. So again, this old

literature, 1990 this paper comes from. So there are lots of indications that additional information can bring you more insight than is possible through the limited information we have through standard ECGs.

The PTCA example, the angioplasty example I showed you in a movie form already, here's another study performed, again, some years ago. This came out in 1989 in a conference proceedings. Here are spatial distributions. So picture this rectangle being sort of wrapped around the body. And the peaks of this surface showing elevations and the depressions. The low points in the distribution showing the syncing of these ST-segments. This transition here you see from the normal QRS-T morphology of the ECG to have elevated ST-segments or depressed ST-segments.

This is a single view, a single tracing, a single ECG lead view of the situation. Here's what you get with body surface mapping, you get a spatial

distribution. So you see where in space there are elevations and depressions that arise during angioplasty.

In these subjects, and again, this was a study performed on patients, in these subjects were able to differentiate between what a normal person looks like to occlusion differences in the three major vessels in which angioplasty typically occurs: The circumflex artery, the left anterior descending artery and the right coronary artery. And you see here that the maps, these distributions are dramatically different for different patients in whom different vessels were occluded. And hence, the ischemia arose in different regions of the heart.

And there was some analysis that was possible from these data to minimize the -- to boil the content down if you will, and identify through the basis of two simple coefficients, extracted from these larger data sets, in which to identify those patients who

are having an inflation of the right coronary artery, the circumflex artery and the left anterior descending artery.

So it was able to differentiate patients, first identify that they were having an ischemic episode and then differentiate where those ischemic episodes were actually occurring in the heart. Again, this is old data, this shows the potential when you have much more information.

There are lots of questions. Is all the information equally good? Are there particular sites on the body that are very sensitive to those changes that come about through myocardial ischemia? There are papers like this one from Fred Kornreich, and a number of others, to identify the best electrocardiographic leads for diagnosing anterior and interior myocardial infarctions. And they used a statistical analysis approach to extract from the body surface potentials those leads with the most power. With the

most diagnostic ability.

And there are other papers like this. There are reduced and optimal lead sets that physicians, and in this case nurses, have proposed. How many leads are necessary for reliable reconstructions. There are lots of these questions about how much information can we really use? And it tends to be very condition-specific. Myocardial ischemia is different from atrial fibrillation, as we see here. The number of leads will be different. The location of those leads will be different.

But there's every indications that additional information can improve diagnostic efficiency. And there are papers, like this one again, that show the use of an unusual configuration of leads. These red dots here show the actual electrodes. The triangles show you the standard ECG lead placement.

By using those additional red dots or using those locations shown by the red dots as electrode locations it was possible in a

number of patients in this study who were non-diagnostic, who did not show up in standard ECG as having ischemic episode and were later found to indeed have suffered a myocardial infarction, in exactly that scenario I described at the beginning of an emergency room diagnosis based on otherwise indications for myocardial infarction.

It was possible from these leads even to estimate the body surface potentials. Here again you see maps showing positive potential as red, negative potential as blue for different patients in each one of these rows being able to characterize the events that those particular patients were going through, in terms of the elevation, the red, and the depression, the blue, distributed over the body surface.

And so additional information is possible. It's possible to use that information to improve diagnostics. More electrodes take more time. There are a number

of different electrode systems and this technology even affects the EEG, recording of EEGs, from the surface of the scalp.

Applying this technology certainly takes more time. That is one of the down sides to using this in a practical clinical situation. But I want to end on this chapter with a summary that came from the Aetna Clinical Policy Bulletin on body surface potential mapping that came out last year, in which those authors concluded that the reliability and test performance of body surface mapping in coronary artery disease is promising. The limited evidence that is available demonstrates proof of concept. However, that further research is needed to better characterize the performance characteristics of these devices.

And I think that's the summary of the state of the art as I see it in terms of purely signal-based analysis, looking more or less directly at the electrocardiographic

signals that come either from a standard ECG-lead or these additional electrodes or the body surface potential mapping.

Now we come to part two of the story, which is how additional information, that we get from the body surface, can be combined with additional information that we get from the physics of the problem, from the physiology of the problem, to further enhance and further improve the diagnostic potential of any approach like this that uses this inverse approach to body surface mapping to electrocardiography.

And so we have here three circles. The physical laws, physiological constraints and the torso geometry. And I'll about each one of these individually. The body surface potential maps I just showed you are the input. They come in through the physical laws. They're the data on which we start to apply the physical laws that can then tell us more about the underlying cardiac electrical

activity based on the measurements we perform on the body surface. That's where the physics comes in.

The torso geometry is something that's relatively easily available to us today in the age of modern imaging technologies. CT imaging, MRI imaging of the whole torso can provide additional information about the location of the heart. The location of other organs within the torso. And that information, again, helps improve the diagnostic power of that raw data that's coming form the body surface.

And then we have physiological constraints. And I'll talk more about those and how we use those a little bit later on. Now generically you can picture this domain that I'm going to try and get you through, without too much pain, as being based on the notion of a source, the heart in our case, and remote measurements from that source. The remote measurements being the body surface

potential, the ECG that we record from the surface of the body.

And the relationship between them is clearly, as you can imagine, determined by physical law. The way current flows, the way electricity is distributed in the body in a conducting volume, is something that the physics of electricity helps us to find. And so we know those relationships from physical perspective.

And the whole goal of the inverse problem is it to take the information available on the body surface and then go back to the heart. Identify features of the heart from that, again, non-invasively acquired body surface information.

The forward problem that is always associated with an inverse problem is the reverse. It's the very, you could say, obscure or hypothetical situation in which we know the electrical activity of the heart and we predict the ECGs from that. That's the

situation that never arises clinically. But it's part of the physics of the problem, it's part of how we address the problem.

So one part of this big problem is called the volume conductor model, that's the torso. That's where the torso geometry comes in. The other part, the part you see on the left, is the source representation. This is, again, where it gets important -- tricky but importantly tricky. And we'll talk a lot more about sources in general. I showed you before how the dipole is the simple source that we use when interpreting standard ECGs and then we have a more distributed source when we try and interpret the more rich information available from body surface maps.

And the sources can have different forms. Here is the dipole source, schematically indicated here as a single entity representing the electrical activity in the heart. It moves in time, it can shift around. It can change its amplitude in time.

So you've got an ECG that is a time signal. That's one of the sources that's possible.

Another source that we use a lot is the capturing of the voltage on the surface, the outer surface, of the heart. That's what this is meant to indicate here. So what are called the epicardial potentials, or pericardial potentials. The potentials on the outer surface of the heart.

And then there's another version of a source, which captures the spread of the wave of electricity. The heart works by generating an electrical wave followed by a mechanical wave leading to contraction. And we can characterize that electrical wave and capture that progression of the wave itself. And also represent that as a source. And those all indicate ways that we can generate signals.

And there's a fourth representation I'll show you in this particular diagram. So here you have a table,

and I'll walk you through this and we'll just hit the important pieces, of these different sources. So the dipole. It's the simplest source. It needs very few leads to capture. It's the conventional source. It's the one that the ECG is based on.

One of the questions we'll have to deal with, and I'll come back to this in two slides from now and try to get this point across to you, is solving these inverse problems is very challenging. It's mathematically and computationally challenging. It's a hard problem. And I'll try and capture some of the difficulty, because it's really at the core of these technologies that you're being asked to evaluate. It's a difficult problem for a number of reasons. And one of them is that the information you have the body surface may not uniquely tell you what the associated electrical activity at the heart, and within the heart, is.

And so that uniqueness of the solution, which has lots of mathematical definitions and mathematical consequences, also has sort of a fundamental intrinsic meaning, a qualitative meaning I want to try and convey to you.

You want, of course, to be able to identify uniquely the location of the myocardial ischemia from the body surface potential. It does not help if the solution comes back like those old quadratic equations that we all used to solve in high school with two solutions. Right? When you solved the quadratic equation you get two solutions in algebra and you have to use common sense or some other information to decide which of those two solutions is actually the correct one.

This is a situation that is obviously not tractable in a medical situation. It's not enough to tell a patient, well there are two possibilities and we're

going to treat them both or we're going to guess. Or we're going to flip a coin. We need to have unique solutions. And so uniqueness is a key criteria.

So the dipole can lead to unique solutions, but only with substantial additional constraints. We have to really impose major constraints on the source before we get unique solutions. The epicardial potentials have many advantages over the dipole. They are more complex, they capture that additional complexity. They are quantities we can measure. There is no dipole meter. There's no device you could put on a patient or even if you could access a patient's heart, to capture a dipole though direct measurement.

Epicardial voltages you can directly measure in invasive procedures obviously, or with catheters. But it is possible to measure those potentially. This leads to a unique solution, at least

mathematically unique. It turns to it's hard to really capture all that uniqueness, but it's possible. The interpretation can be ambiguous. This is still a surface measurement for activities that can very often exist within the heart itself. And so we have to then go another step of taking these surface potentials on the heart and interpreting those in the context of underlying cardiac activity. And that is fraught with its own set of challenges, but is certainly doable.

The problem is ill-posed. And we'll come back to that again. This has to do with, it's related to uniqueness.

The epicardial/endocardial activation time is also a quantity that's measurable and clinically directly useful. The clinical procedures that happen today to examine a heart with catheters are based on identifying the passage of the wave front through the heart itself.

Catheters, sometimes with multiple electrodes embedded in them, are placed inside the heart and outside the heart to capture that wave of activation. And to capture abnormalities in that wave of activation. That's mostly how arrhythmias are detected and how they are ultimately treated in modern electorcardiac electrophysiology. And so this is a very reasonable source. A very laudable source, a very sensible source, clinically.

The uniqueness of this problem has never really been proven. It's still unclear. There are assumptions necessary, somewhat tenuous assumptions that one has to impose to even solve the problem. And, again, it is ill-posed. We'll come back to that again.

The most modern approach is really the one that goes back to the earliest ideas about cardiac electrophysiology, and even nervous system electrophysiology, and that's the transmembrane potential. This is the driver. This is the electrical source in the

heart that we're talking about ultimately here. And it's possible to formulate the problem in terms of transmembrane potentials. And this is, in many regards, now becoming the most modern formulation and I would argue the most relevant formulation for this particular problem of myocardial ischemia and detecting it, because action potentials change between a healthy situation, the black line here and an ischemic action potential, schematically captured in that blue line.

And so an inverse solution, a source representation based on those sources, those metrics, those changes at the cellular would seem to be, and is naturally, a very attractive one and we're able to measure transmembrane action potentials in cells. We can't measure it in patients, cells are very small. We need very small electrodes to measure or we need fancy optical techniques to do this. But it's possible to measure them.

The solution is not unique.

Clearly not unique. But it appears to respond well to sensible constraints. It appears to have practical solutions even though mathematically it's not as clean as, let's say, the epicardial potentials that do have a mathematically unique solution.

So these are the sources that are relevant. And now you've seen sort of the sources. Now in some sense I'm going to take a step backwards and explain to you why we even care about electricity in the context of coronary artery disease and myocardial ischemia. And that goes back to a picture like this, which shows what happens unfortunately as we age and eat bad things. Atherosclerosis will build up plaques in our vessels and ultimately, either through a clot or through a vasospasm, we lose blood flow into a certain region of the heart and that region of the heart suffers, as I've just explained to you, changes in the transmembrane potentials in those regions that are affected

by ischemia. Those changes result in electrical differences.

The action of potential amplitude is different in one part of the heart than it is in another part of the heart. And that's the magic ingredient to have current flow to produce voltages, to produce changes that we can see on the body surface.

So here's the cellular explanation. Here's the explanation at tissue level. Here's a chunk of left ventricular wall, let's say. And the gray region in the middle we're indicating as being ischemic. The blood flow is inadequate to get to that part of the heart. The action potentials within that region have truncated amplitude, smaller amplitudes than the nearby neighboring healthy cells. And the result is current that flows between those two. There's a voltage difference between this and this. And so during this phase of the action potential. This phase of the ECG down here, shown by this

vertical line, we get current flowing from the healthy tissues intracellularly into the sick tissues. And depending on where the ischemic zone is we can get current flowing in different directions. So those light blue lines can take on different orientations depending on where the ischemic zone is. And those different orientations of current flow are reflected in a very simple minded way through things like ST-segment depressions, here, or ST-segment elevations here, that are traceable, detectable on the ECG.

This is how we do anything with an ECG to begin with, in the context of myocardial ischemia. So this is the transition from perfusion to electrical abnormalities, which is the basis of all these approaches you'll be evaluating today.

So when we put all this together it's possible to solve these inverse problems. It's possible to capture the sources. In this case it's an epicardial and endocardial

activation time source. So the colors here correspond to time, not to voltage.

This shows a heartbeat. Here are the outside surfaces, the epicardial potentials. Here are the -- I'm sorry -- activation times. Here is the activation time on the inner walls of the two chambers, the left and right ventricle. We have a geometric model indicated here schematically as a slice through the torso showing the various boundaries of tissues like the lung and the subcutaneous muscle and fat. And then we have body surface potentials.

And if we know this information and know the geometric model we can predict the body surface potentials. That's the forward problem, this artificial problem. The hypothetical problem. The clinically relevant problem is the reverse. Going from the body surface potential back to the sources. And that's what we're really setting out to solve.

So how we do this? What are the

steps involved? What does any technology that you're going to look at that's going to try and solve an inverse problem include?

So it starts with image acquisition. You need to have the geometry. You need to know the source of the model. You need to take from that image structure. You have to identify the heart, the lungs, whichever tissues are relevant to your particular implementation of this inverse problem. You have to identify that. From that information you have to build surfaces that describe those inners. You may have to include discrete points, measurement points: where do the ECG electrodes fit relative to the rest of the anatomy of the thorax? That has to be included in the story.

Then you have to build models. Of volume models, this is called meshing in the technical term. This is building discrete models built based on polygons that give you something a computer can actually work with.

Without those discrete models computers can't really start to deal with the problem.

Then you have to apply these parameters and boundary conditions. Boundary conditions mean what is the voltage on the body surface? That's a boundary condition. There are other boundary conditions you're going to impose inside the body. And those all have to be part of the modeling. And you apply those boundary conditions. And then eventually, of course, if you're going to test something you have to verify it and look at parameter sensitivity. And then that whole thing sort of feeds back through the measure data. So this is where the body surface maps finally come in. They come in as applied boundary conditions. They get fed into this part of the problem.

It all sort of comes together to solve the actual problem involved, and there's even feedback possibilities depending on how technical and how sophisticated you want to

get in this problem. You may want to change the meshing, for example, as a function of these solutions that you're actually receiving. So you may say there's a source of interest I need to identify in the heart. So let's put more elements, more nodes, in that region so I get more accurate representation of the electrical activity in that particular region.

So there's a lot of sophistication, a lot of interaction here that's possible, and then throughout it all, as you've already seen, we need visualization tools to see it all. So that's sort of really the technical question.

Now comes what arguably is the most difficult thing about this whole problem, the one I've been warning you about for awhile now. And that's what does ill-posed mean. How do we capture that? Because this really is at the heart of the answer to the question of why this is a hard problem. Why it's taken

so many years to even get useful solutions.

And you can look up in lots of journals like this, there are whole journals on ill-posed problems. This is a well known terminology from physics and mathematics. But, again, I'm sure most of you don't have an inkling what that is.

If you look up the conditions for ill-posedness or for well-posedness, there has to be a solution. The solution has to be unique and the solution has to depend continuously on the data in some reasonable topology. That sounds quite mathematical. Ill-posed problems break one of those three rules, and you only have to break one to create a problem that's ill-posed. Okay? So that probably tells you also next to nothing.

Here's another graph, that again, tries to capture this schematically. You may have measured information like this. If you have an ill-posed problem it turns out that the solution, or the exact solution, is almost

impossible to actually define, because of the nature of this ill-posed nature.

And again, this is probably not going to help you as much. Now, the last piece of this figure, which I hope does help you, is perhaps the simplest and the cleverest of all.

And this is this cartoon. So the situation is the following. Our knight here, our brave knight, aboard his hobby horse has come upon some tracks in the sand and is trying to picture from those tracks what sort of animal must have made those tracks. And he knows from his previous knowledge, being a hunter and fearless and with lots of experience, that there are various creatures that he has to worry about encountering, some more deadly than others, and they each have different footprints. Right? They each have different footprints. You can clearly see the difference of these. When you line all three of them up together they look different.

The reality of the situation is that if he can identify this footprint than he can uniquely determine which animal made that footprint and how worried he should be. Whether this is a free meal he should be going after or whether this is a terrible threat and he should be turning around and running the other way.

The problem, however, is that the footprint doesn't clearly fit into any one of these three categories. The footprint has noise. The footprint has imprecisions, because footprints are never perfect. The sand has been there for awhile, they got a little smudge. The animal moved its foot as it was leaving, whatever. There are always sources of noise in real measurement.

And so because of the noise of the measurement he's not sure. He's not able to uniquely determine which of these three animals he's likely to encounter if he follows those footprints. And that's really, in a

qualitative way, a very high-level way, what makes this problem very difficult to solve.

Small fluctuations in the electrocardiogram can lead to dramatically different interpretations when it comes to the underlying identity and localization of the ischemic region, let's say, in this particular setting. So that's really what ill-posed means.

Now how do we get around this ill-posed nature of problems? Again, we combine forces. We join equations that really summarize the physical laws of the questions involved. We include torso geometry with some amount of sophistication. It's an open question how much sophistication we need. And then we apply physiological constraints.

Now physiological constraints are sensible limits that we can set. They are the things that say, we know that the voltage, the signal amplitude on the heart, can only be so large. Anything bigger than that just isn't

real. It isn't physiologic. And so we can exclude it as a possibility.

And so we can apply constraints like that to limit the scope of the problem. To identify this region somewhere in the middle that meets all of these requirements and we deem to be a useful solution. That's really at the heart of this whole problem.

So there are different ways of applying constraints. There are closed forms that lead directly to some equations I won't burden you with. Through some weighting coefficients, here this little lambda here is a kind of magic coefficient that we slide around and we adjust based on our physical knowledge and our physiological constraints.

And that allows us to identify a unique solution point coming from all three of these directions. And we identify a single point in that solution space and say, that's the best solution. Based on our information today that's the best solution I can give you.

That's one approach to doing it.

Another approach to doing it is iterative. Here we have an iterative algorithm where we guess the solution. So we guess something about the heart. We say, here's where we think the ischemia is. And then we solve that forward problem, which is an easier problem. It has a unique solution. We solve that forward problem and then we compare it with the measurements. Here's the body surface measurements, we calculate that difference and if that difference is small, we say oh, we're close. We're close enough. And if it's not small enough then we keep going around and around in circles and keep guessing. Keep making new guesses. And this is generically an iterative algorithm and this is how a number of these systems work that are used today.

And ultimately we get an answer that is the best answer, but it's not the only answer. We don't have this notion of a single

correct answer. We have a notion of an answer that fits somewhere in that solution space and that we sort of step-wise approach it wandering a little bit through space, through our solution space and get to somewhere inside. But as long as we get to any point inside this region we consider it a good enough solution. It's as good as any other solution given the constraints we have. Yes?

DR. GOODMAN: Five minutes. Thank you.

DR. MACLEOD: So finally just a few results of where the field is and what we've been able to do. I've showed you this result before, I won't bother you with that again.

I'll show you some more up to date results. And this is from 2007 from the group, what's called the Simula Research Lab in Oslo. Here we have a slice through the heart. Here's the left ventricle, right ventricle. This red region here was made

ischemic. It was produced to be ischemic in the model, this is a computer-driven process. That heart was then placed inside a realistic human geometry. Body surface potential maps were calculated. Noise was added. And then from those body surface maps these researchers attempted to reconstruct this picture. So the goal was to make a picture that looks just like this.

This is as close as they got. So you can see there's something going on there. There's something localized in the same region that's localized here. The amplitudes are way off. This was bright red, here it's sort of pale green. And that's about as close as they got.

Here's another solution, a more modern version, 2010, from the same lab. Here again is the true ischemic source. And here are different approaches they've used. Here they're actually comparing different approaches and different constraints. And

different assumptions about the noise levels, about the uncertainty of the body surface measurements. And again they're able to identify something in the region where the ischemia was created for sure, but it's a little too small compared to the actual extent. The amplitude is somewhat different from the original one. And so there's still errors.

We've done, and other groups have done, experiments to generate data. To test out these ideas and test out these approaches in which we've taken animal hearts, suspended them in human torsos, or human shaped torso tanks in which we've recorded the body surface potentials, recorded potentials within the heart itself using needle electrodes. We get images like this that show the tank surface, inside the heart. Inside there the ischemic zones that we actually are able to measure. So we produce ischemia in real preparations. We occlude coronary arteries through this

cannulation system and generate localized ischemia.

And one of the things we've discovered is that ischemia happens in strange and wondrous ways. Sometimes it happens in the middle of the wall, as you see here and here. Sometimes it happens here on the middle of the wall over there. Sometimes it happens in a more subendocardial region, right here. These are all slices through this individual heart.

So we're learning more about what ischemia actually looks at the cardiac level. And we're able to now use modeling approaches. And these results are not in the slides I gave you because they were generated two weeks ago. So this is the most recent results I know about in this domain. This shows the extracardiac potentials and those transmembrane potentials I talked about before from measurement. Those were measurements in that preparation I just showed, inside

animals. We, again, measured body surface potentials, added noise and calculated the inverse.

So the idea is that this picture should look a lot like that picture. And this is the situation with sort of a little bit of noise added. Here is a little bit more noise added. What you see here is we're doing a pretty fair job of identifying regions of ischemia, even regions that are within the wall, within the space inside the left ventricle, not just on the surface. And we're able to do it even in the face of a range of noise levels. So this technique is relatively insensitive to noise.

And so there is progress here. There is tangible progress and a lot of recent interest in solving this problem. So now we come to the bottom line. Now we come to the really the summary slide, the money slide for you folks is, is this technique ready for prime time? And Susan really pushed me hard

to say something about this.

And it's a little bit like the iCloud, right, we know it's out there and those who are Mac users, are sort of tentatively looking at it and saying can we risk it. Will we lose all of our data if we put it in the cloud and what happens if it rains. You know, all these things are scaring us, but there's a big question out there and the same is true here.

So this field has a long history. It's not quite prehistoric, but it's been around for a long time. And as you've seen with some of the things I've showed you there's been a lot of thought about it. It is a hard problem. But like many hard problems there are a range of possible solutions. From the simple-minded ones like this to very sophisticated ones. So this is a problem that actually has solutions and I would argue that this is a classic situation of unrealized potential at this point.

There is clearly a way to solve this problem. There is clearly a need to make progress in this domain. And what we need now is to apply some of these techniques that I've showed you that are truly research techniques that have not been used in clinical applications and to begin to apply them to patients and begin to explore their utility and to update our knowledge, if you will, our application of this technique to human studies.

And with that I think I'll close the information part of the talk and just point you, should you be interested in this, in an application in a program that's freely available. It's open source. This is not my software. This comes from colleagues. This is a tool that allows you to explore this whole question, to make ischemic changes inside the heart and see what their consequences are in body surface. So if you actually want to explore the behavior that

we're talking about here this is a great lightweight, easy and accessible way to do that.

And with that I'll close. And thank you for your attention. And be open to any questions you have.

DR. GOODMAN: Thank you very much, Dr. MacLeod. It's always good to have that does of electrocardiology in the morning to get going. We appreciate that, if our coffee didn't do the job. Do we have a concise question at this point for Dr. MacLeod before we move on? Yes.

DR. JANOWITZ: It seems to me that this problem is very similar to image reconstruction used in CT and nuclear medicine technologies and, obviously, it's very important to make measurements of conductivity or individual geometry if you're going to solve the back reconstruction or the iterative reconstruction.

Do any of these devices actually

make measurements of conductivity or anatomy? Or are they just looking at the surface potential?

DR. MACLEOD: Yes, that's a very good question. So you're right, it is very similar. I talked a little bit about ill-posedness, the reconstruction problem of imaging is better posed, or less ill-posed. So it tends to have more stable solutions, but it is a very similar mathematical problem.

The question you asked about electrical conductivity is embedded in the whole field of impedance tomography. And a lot these same equations apply and a lot of these same constraints apply. And, you know, we actually it turns out right now, are building models to help physicians use impedance changes as a way to measure changes in things like profusion ventilation mismatch in patients with pulmonary disorders, for example.

So there's a lot of similarity in

these approaches in the underlying math and physics. And we, indeed, have to have geometric information in order to capture the changes in conductivity, just as we have to include conductivity information when we're solving this particular problem. And the problem is certainly sensitive to those conductivity assumptions.

DR. GOODMAN: Yes, and by the way the question was from Dr. Janowitz. Dr. Heseltine, do you have a quick question?

DR. HESELTINE: Pete Heseltine. We're being asked to consider the questions for two populations. One group who are asymptomatic, who have coronary artery disease. The other who are symptomatic.

Even allowing that that's a continuum, what empiric data are there to support electrocardiography as a way of identifying individuals who have coronary artery disease who do not currently, at that time, have ischemia?

DR. MACLEOD: Yes, that's a very good question. If there is no ischemia present then, by definition, there are no electrical changes. There has to be a transduction from a profusion problem to an electrical consequence. And so there has to be something that reaches a threshold of blood flow below which electrical changes start to arise. I know of no connection between coronary artery disease and changes, let's say in action potential morphology, to come purely because of the underlying disease substrate.

So there has to be something that would induce those electrical changes. The cases that are reported of patients with coronary artery disease who do not test positive for standard electrocardiography, and yet do test positive in the application of body surface mapping, again assume that there are electrical changes occurring, be that through some sort of pharmacological stress or physical stress, but that those changes are,

again, either in regions not detected by standard electrocardiography or are sub-threshold to standard electrocardiography and so are detectable by these more sophisticated approaches. But there has to be an electrical event because this process detects electrical behavior.

DR. GOODMAN: Okay. Thank you very much, Dr. MacLeod. By the way we'll want to have you available for the balance of the day. And when we get into our panel discussion we may have further questions for you at that time.

DR. MACLEOD: Great.

DR. GOODMAN: Thank you very much.

DR. MACLEOD: Thank you.

DR. GOODMAN: Next is Dr. Jerome Fleg who is a medical officer at the National Heart, Lung and Blood Institute, which is part of the National Institutes of Health in nearby Bethesda, Maryland.

Welcome, Dr. Fleg. And I'll just

show our panel that we did get, ahead of time, a copy of his presentation. You may want to refer to that as well. Welcome, sir, please proceed.

DR. FLEG: Thank you. I'm going to switch gears to the clinical front. As a trained as a clinical cardiologist I still see patients one day, even though my full-time job is at the National Heart, Lung and Blood Institute doing clinical trials.

So what I'm going to do is try to take you through our diagnostic evaluation of patients who are suspected of having coronary artery disease. And a patient that might come into your office that you would want to do a workup for.

First of all our standard definition of coronary artery disease is by coronary angiography, this is kind of the gold standard as I will refer several times throughout my presentation. And various definitions are used. Either 50 percent,

sometimes people will use a 70 percent diameter reduction of at least one of the three major coronary arteries, or their major branches or the left main coronary artery.

In the left main 50 percent is standard. As I say, for the other three arteries, the left anterior descending, the circumflex, the right coronary definitions range, usually it's either 50 percent or 75 percent.

Remember though, a 50 percent diameter reduction actually area wise is about a 75 percent area lumen reduction. And so, you know, during any type of stress, physical or pharmacologic, that's going to usually impair blood flow.

Well what are the clinical manifestations of coronary disease? We have three. Of course it can be asymptomatic, let me say that, as was mentioned or referred to in a previous question.

But the major presentations are

these three. Angina pectoris, which is a substernal chest pain due to reversible myocardial ischemia. And it's either induced by increased oxygen demand to the heart or reduced coronary blood flow, or a combination of the two. So if you're walking up a hill and you've got narrowed coronary arteries, you're increasing the demand, you might get ischemia. If somebody has exposure to severe cold they may get some coronary constriction. Or if they're very angry, that may also do that, in which case you'd have a decreased supply.

Second manifestation is acute myocardial infarction. And I guess my secretary was a little nervous because she wrote myocardial neurosis, that should necrosis, induced by a complete occlusion of a coronary artery, usually due to rupture of an atherosclerotic plaque. And obviously, this is a feared complication because this has a high rate of death, although we've done very

well in recent years in bringing down that rate. A large percentage of patients, unfortunately, do not make it to the hospital. Those who do, the mortality rate now is as low as five percent, so that's about one quarter of what it was three decades ago.

And then, obviously, the worst manifestation is nature's way of telling you to slow down, sudden cardiac death. Death from a cardiac cause, in this case coronary artery disease within an hour of the onset of symptoms. And this is usually due to ventricular fibrillation caused by either acute myocardial ischemia or infarction.

And unfortunately many of these patients do not even make it to the hospital to be treated. The incidence of acute myocardial infarction about a million cases annually in the U.S. and sudden cardiac death 200,000 to 400,000. So these are both highly prevalent conditions. The number of patients living with coronary artery disease in the

U.S. is estimated to be about 16 million. Those would be people who had either a previous infarction or never had infarction but just have evidence of coronary disease.

I think most of you are probably familiar with the major risk factors. But when we're taking a medical history this is a key in addition to, of course, seeking the symptoms of angina or a history of myocardial infarction. We certainly delve into whether they've got risk factors that would put them at a high risk for developing CAD.

Older age, male sex, a positive family history seems to have an important role, even independent of the modifiable risk factors. Hypertension, elevated LDL cholesterol. I didn't write on there, but also low HDL cholesterol, since HDL is the good cholesterol, low HDL is a risk factor. Oh, I do have it here. Smoking, diabetes, obesity and physical inactivity.

So the more of these risk factors

that you have the higher your chances of having coronary disease. Even if you have no symptoms. And I would point out that in general if you did coronary angiography on 100 people who were in their 60s and 70s about half of them would have probably at least one vessel that had close to a 50 percent or more blockage.

So people who are presenting with clinical coronary disease probably represent about half the people who actually, in the community and general population, have evidence of coronary disease if we did a coronary angiogram.

Okay. When we're trying to diagnose is this really angina pectoris or is this just some type of chest wall pain, or pain due to pulmonary problems or other issues. And we look at four issues mainly, or four features. The location of the pain, the character of the pain, the precipitance and the duration and the precipitating or

relieving factors.

And so the location of angina is usually substernal but sometimes it can be in the neck or the jaw. A lot of times it will start in the chest and radiate to the neck or the jaw. Patients will classically define it not as a pain but as a discomfort. As kind of an oppressive sensation. Tightness, heaviness, squeezing are also common descriptions. And some patients, particularly the elderly and those with diabetes may not even have pain. They may have what we call anginal equivalents, which is shortness of breath, dyspnea and less frequently nausea, weakness or presyncope if they actually have a decrease, if the ischemia is severe enough to cause a decrease in pump function.

The common precipitance of angina will be either -- these are things basically that either cause a increase in demand for the myocardium, a decrease in supply of oxygen or the coronary blood flow or a combination. So

exercise is mainly increased demand. Emotional stress can be a combination of some increased demand and some coronary constriction. Cold temperature would probably be more coronary vasoconstriction. Meals because they cause an increased demand for blood to the G.I. tract, cause an increased demand. And smoking, a combination of both because it stimulates catecholamine release, which elevates heart rate and blood pressure. Also nicotine is a coronary vasoconstrictor.

The duration of relieving factors, typical angina lasts three to five minutes. If somebody says, oh yes, this pain lasts about an hour you can almost guarantee that that pain is not anginal pain or if only lasts for two or three seconds, similarly. So the duration of three to five minutes is pretty typical.

If the pain lasts more than 30 minutes, and we really do think it's coronary type pain, then that suggests that there's

some myocardial necrosis taking place, because usually after 20 to 30 minutes ischemia will result in some loss or death of myocardial tissue. So that patient obviously needs to call 9-1-1.

Relief by rest or sublingual nitroglycerin are the two classic relieving factors for angina. Most patients if they pretty mild when they stop within a few minutes, within usually five minutes the pain is gone. A response to nitroglycerin is also rapid, usually it's within a minute or two. Maybe as long as five minutes.

I would point out that nitroglycerin can also relieve esophageal pain, so it's not totally specific. Just because your pain is relieved by nitro doesn't necessarily mean that it's from your coronary artery disease.

If you just focus on the right two panels of this. These are data from the Coronary Artery Surgery Study, which was a

study that was done back in the late 1970s, ancient history now. But some lessons that are still valuable. The right two panels look at the chances of having either a left main or three-vessel coronary disease as a function of age. And we look at it in men and in women. It's a function of age and then the character of the chest pain. So if you have definite angina, that's the top line. Probably angina is the middle line. And non-specific chest pain is the bottom line.

And so you can see that first of all as you get older your chances just, with a given presentation, even non-specific chest pain when you're in your 60s or 70s, as I mentioned, a lot of those people, 25 percent will probably have coronary disease.

However, as you got to probable or definite angina you can see that at any given age your likelihood of having significant, in this case severe, coronary disease increases dramatically. So that's why a good history is

actually very important. And history is probably, for most medical conditions and particularly coronary disease, probably about two-thirds of the information that you get as to whether they have the disease or not is from your medical history. Obviously location and the degree of disease we need some more sophisticated tests to do that.

So on the physical examination in general it's not all that helpful. What we're really looking for is things that would confirm that there's some risk factors that the patient has elevated risk for coronary disease. Hypertension, coronary arcus, arcus or xanthelasma. The xanthelasma are the fatty deposits around the eyes. And they're usually a sign of increased cholesterol. I read a recent paper, actually just a couple days ago, that even controlling for cholesterol, xanthelasma seems to have some independent predictive value.

Retinal arteriolar changes,

because the retina is kind of a window to the arteries and the rest of the body. So if you had a significant disease there you may well have disease in other organ beds, arterial disease.

Carotid bruit, again evidence of arterial disease. Reduced, absent or peripheral pulses. So actually coronary artery disease is simply the atherosclerotic process in the coronary bed.

Most of these patients will have some evidence even though it may not be clinical, but at least angiographic evidence of disease in other vascular beds, either the retinal vessels, the carotids or the peripheral arteries.

During an acute chest pain episode, if you're fortunate enough to catch a patient actually during an acute episode, you may get some evidence of LB dysfunction. Such as either rales in the lungs, an S3 gallop or mitral regurgitation -- ischemic

etiology, ischemia of the papillary muscle. This, of course, if pretty uncommon in the office setting. But if you're lucky enough to catch an episode you might want to listen for these findings.

The resting electrocardiogram is still, even in this day of highly sophisticated imaging tests, is still a very valuable tool. It's cheap, it's readily available and if you see pathologic Q waves on the EKG this usually, but does not always indicate, a prior myocardial infarction.

Again, no test is perfect and there are other conditions that can mimic an infarction. Sometimes just somebody who's extremely obese or has COPD, you can have for instance, low anterior wall voltage because of the increased distance from the chest wall to the heart.

ST-segment depression is also a non-specific finding unless you see it transiently during a chest pain episode. So

again, if you're lucky enough to catch a patient during and episode of pain, get an EKG there's significant ST-segment depression and then it resolves after the pain resolves then that's pretty good evidence that that patient had myocardial ischemia. That's essentially like a poor man's stress test.

Other non-specific findings that suggest structural heart disease would be finding evidence on the EKG of left ventricular hypertrophy, left bundle branch block, left atrial enlargement, atrial fibrillation. Again, these are not -- doesn't tell you they have coronary disease but strongly suggests that they've got some kind of structural heart disease, although there are some people of course with atrial fibrillation who have low A-fib without the structural disease.

Well, basically then once we have at least a reasonable index of suspicion that a patient may have coronary disease based on

their history. Then usually the next step is to do some type of a stress test to induce ischemia.

And we can use exercise, either treadmill or cycle ergometry. Either with the arm or the legs. Pharmacologic stress tests with either dobutamine to increase heart rate and blood pressure to increase myocardial demand or dipyridamole or adenosine, these are vasodilator so they dilate the coronary arteries. They actually cause a steal of blood from the ischemic region to the non-ischemic region. So they kind of shift the blood flow due to not demand but just differences in the ability to coronary vasodilate.

And then we have less used physiologic maneuvers, such as atrial pacing or mental stress to induce ischemia.

So I'm just going to review now, for the rest of the presentation, basically the diagnostic tools that we have, you know,

the laboratory tools for trying to diagnose coronary artery disease. So we'll talk about using the electrocardiogram, the radionuclide imaging, echocardiogram and a little bit more expensive and less available tools, MRI and PET scanning. And then anatomic, these are physiologic so these are looking actually for inducing ischemia. These are detecting the effects of ischemia and not so much individual coronary artery narrowing. And then we have the anatomic tests, which actually detect individual coronary artery disease.

So we have the coronary calcium scan, which is really kind of a screening test that indicates that you've probably got some disease. It doesn't tell you much about the narrowing of the artery. And then we have CT, angiography and invasive coronary angio, which is the gold standard to which all of these other modalities are usually compared. It's a not a perfect gold standard because, actually, the angiogram tends to underestimate

the actual severity of disease if you do intravascular ultrasound.

When we talk about looking at the test performance of any of these tests we usually use the terms, at least for clinical evaluation, the sensitivity, specificity and either the positive or negative predictive value of the tests. And I think most of you are probably familiar with these terms. But basically sensitivity is the percent of persons who have a disease who are detected by the test. So it's the true positives divided by the true positives plus the false negatives. That should be a plus.

The specificity is the percent of persons without the disease who have a normal test. So it's basically like the converse of sensitivity. True negatives divided by the true negatives plus the false positives. So if you have a test that has a lot of people that have positive tests that don't have the disease then that test has a poor specificity.

And then positive/predictive value is simply the true positives over the true positives and negative predictive value, the true negatives over the total negatives. So in other words, a positive test -- a test would have a good positive predictive value if there were not many false positives. So that most of the positives that you saw were true positives.

Now, when we're doing a test any of these diagnostic tests that I will cover next, after showing this slide. Basically what we're doing is we're taking a patient who is appearing on the dashed line here. Who presents to you with the dashed line and their pre-test probability of coronary disease in ten years is indicated here on the X axis. And then the post-test. We do a test and we hope that we can either move that patient down to the lower line, to essentially rule out disease or make it extremely low probability or to move them up to a substantially higher

probability of disease so that then we have much better reason to go and do an invasive test, like a coronary angiogram, to prove both the presence of disease and the extent.

And so a good test will then enable you to take a patient who presents with a certain set of symptoms, that he has the pre-test probability, and move them either lower or higher to either say they don't have the disease or there's a pretty good chance they have. Notice that here in this case even a positive test, if somebody has a very low pre-test probability like 0.1 or 0.15, like 15 percent in ten years, which I guess isn't really that low, that's reasonable risk.

It doesn't mean that having a positive test is an absolute. It still may only raise them up to a 0.4 or 0.5, in other words about a 50 percent probability. But it's certainly much different from having a negative test.

So first we'll talk about the

standard treadmill exercise test, which can also be done of course on a cycle odometer. We used graded exercise through exhaustion. A positive test is defined as a flat or down sloping ST-segment depression of at least one millimeter. And the sensitivity of this finding for coronary disease is about 65 percent at, you know, the numbers I'm going to give you are general averages from multitudes of studies. Specificity is around 708 percent. But if someone has an abnormal resting electrocardiogram the specificity can be much lower. And, in fact, if somebody really has a grossly abnormal resting electrocardiogram with ST-segment changes at rest, then we would probably go to an imaging test right off the bat, because the specificity is just so poor that it's not going to tell you much.

The advantages of treadmill exercise are, of course, it's low cost, it's widely available and there's no radiation

involved. But some disadvantages, as I pointed out, the sensitivity and specificity are only moderate. And it cannot localize or quantify ischemic regions.

Now I don't know, some of the speakers that follow me will probably have some of their new technologies that can do that, but at least with the standard 12-lead stress electrocardiogram, its ability to localize or quantitate severity of ischemia is very poor.

And this is just an example of a classic causative stress test. So patient has a nice, normal ST-segment there in V4 at rest.

Two minutes 50 seconds into exercise they've got about a millimeter and a half or two millimeters of ischemic ST-depression, which increases by another millimeter by four minutes and 30 seconds, which I don't even know if that was peak exercise because the heart rate here is only about 90. And then in recovery you can see

that there's still ST-depression, but it's less than there was at 4:30, if you took one at say six or eight minutes post-exercise hopefully the ischemia would be resolved. So this is a classic positive of treadmill ECG.

Now stress echocardiography a tool that we use quite a lot. The most common tools we use, other than stress EKG, are either stress echo or stress radionuclide imaging. Those have been kind of the, at least in the last decade or two, those have been the main workhorses. Now newer technologies are coming and perhaps encroaching on their territory.

The stress echo can be used with either exercise or pharmacologic stress. So we can use it either with dobutamine or adenosine, dypridamole. Or in a patient who can exercise we prefer to do the exercise because we get a lot of information actually about the patient's prognosis just by how long they can actually exercise. So exercise is

always preferable to a pharmacologic stress test. Sensitivity of stress echo, actually that number should be about 80 to 90 for sensitivity. And the specificity about 85 to 90 percent. It's certainly more sensitive, and also more specific than the stress EKG, because we're actually imaging the test. A positive test is a new regional wall motion or abnormality in the left ventricle that was not present at rest, evidence of inducible ischemia in the left ventricle.

The stress echo is widely available. There is no ionizing radiation, which is an advantage. And it's got very good diagnostic performance, as I showed you there. In addition it detects other structural abnormalities. So if you're looking for valve disease, pericardial disease and even dilation of the aorta, you know, you get a lot of extra information. So a stress echo is actually a very useful tool. A resting echo is bread and butter.

DR. GOODMAN: About two minutes.

DR. FLEG: Two minutes? How much?

DR. GOODMAN: About two minutes.

DR. FLEG: Okay. This advantage is that it's subjective and it depends on the reader expertise. And suboptimal imaging in elderly, obese or COPD patients, which is a lot of patients these days.

That's just an example of an abnormal echo. You see the baseline, left ventricle toward the apex, which is at the top, is fairly narrow. You give the dobutamine, it starts to widen out, this is evidence that the ventricle's contraction ability is reduced. Recovery it's squeezing down better again.

Radionuclide stress testing. Thallium scan or technetium is our most common isotope. Positive test is reversible profusion defect. So again, we're looking at not the actual coronary arteries, we're looking at the blood flow to the heart.

Sensitivity of this is about 80 to 85 percent and a little lower specificity than the echo, about 70 to 75 percent. Some people without coronary disease, like just left ventricular hypertrophy, can sometimes have profusion defects. It's widely available. The computer assisted reading helps to decrease the subjectivity.

Disadvantages is the ionizing radiation and, it too, has reduced performance with severe obesity, women with large breasts can get a breast artifact, or left bundle branch block branch can sometimes cause an abnormality.

This is an example of a classic thallium profusion defect. This is the left ventricular wall. There should be almost like a two-thirds of a circle but the left-hand side of that circle is missing. You can see on the delayed scan, after the patient has rested, there is some filling in of the septal wall, which has ischemia, it still hasn't

totally filled in. And as I said, computer assisted images.

I'm going to skip magnetic resonance imaging and electron CT. I'll just do a couple more slides here. The computerized tomography CT, this defines the coronary anatomy. And this is not the regular invasive coronary angiogram, this is peripheral injection into an arm vein. And has very good sensitivity, 90 to 95 percent, and very good specificity. So it's very good in ruling out coronary disease. Disadvantages is that it does require a significant radiation dose. And usually people need beta blockers to slow the heart rates.

And this is just an example on the left of a non-invasive coronary angiogram with CT. And then the coronary angiogram on the right and confirming the blockage in the mid, left anterior descending artery. Okay. Invasive coronary angiography is the gold standard, as I mentioned. A positive test is

at least a 50 percent reduction in coronary lumen diameter. Advantages, it's the gold standard, the images are high resolution. You don't need a stress test. But it is invasive and costly and a high radiation burden.

So this is a summary of what I've covered. Coronary artery disease is certainly the most common form of heart disease in the United States, about 16 million living with it. High morbidity and high mortality. Sudden death and acute myocardial infarction, the main complications.

Good medical history and exam really guides your work up to decide whether you should do any of these additional tests. And there are numerous either non-invasive or minimally invasive diagnostic tools, which I've gone over quickly here. Anatomic testing, using CT or invasive coronary angiography. And the invasive coronary angiography still remains the gold standard for CAB diagnosis. Thank you very much.

DR. GOODMAN: Good, thank you very much, Dr. Fleg. We appreciate that to cover this subject in your allotted 20 minutes is nearly impossible. The good news is that we anticipate you'll be available for the balance of the day.

DR. FLEG: Well, balance of the morning.

DR. GOODMAN: Just through noon is it, correct?

DR. FLEG: Yes.

DR. GOODMAN: Okay. We may have a further question for you by then.

DR. HESELTINE: I have.

DR. FLEG: If you cluster them that would be good. Or if you need to email me or call me or something.

DR. GOODMAN: Well we have to do our business today. Does anybody have a pressing, concise question now?

DR. HESELTINE: Peter Heseltine. Please tell us what the role of biomarkers in

identifying ischemia is in the symptomatic patient.

DR. FLEG: Biomarkers are usually used to diagnose myocardial necrosis. But I will say that the new troponins are so sensitive that this is really kind of turning everybody on their head, because some people who would otherwise, by our prior lower sensitivity troponin assays, which is the most common biomarker that we use for ischemia detection, would have been negative. With some of our ultra sensitive assays they may be positive.

So the classic definition, at least for the biomarkers as we use them in clinical cardiology, is not to detect reversible ischemia but really to detect myocardial necrosis.

And so on acute myocardial infarction, to diagnose infarction requires a rise and fall of the biomarkers, either traponin or CKMB as the two standards of

myocardial necrosis.

So for an asymptomatic patient, or a patient who just has ischemia, who has angina, we don't even draw those bloods because the classic teaching is that if they have a reversible short episode of angina they should not have had any myocardial necrosis.

DR. GOODMAN: Okay. Thank you very much Dr. Fleg. We appreciate your comments and concise version of a broad ranging topic.

Next up is our technology assessment presentation, which will be coming from, I believe, led by Dr. Remy Coeytaux, is that correct? Yes. And accompanied by Phil Leisy. Thank you.

As they're approaching the podium and we're getting set up with their slides I'll just remind the panel that oftentimes when CMS seeks some information in the form of a systematic review in support of MEDCAC meetings and other coverage-related issues,

though commissioned through the Agency for Health Research and Equality, a technology assessment.

And there are, from one of the 14 evidence based practice centers. A couple of them have kind of a primary assignment to respond to these requests from CMS and this is the group that will provide it.

And so Dr. Coeytaux is the Associate Professor of Community and Family Health Medicine at the Duke Clinical Research Institute. Dr. Leisy is M.D. candidate at the ECU. Is that East Carolina University? Brody School of Medicine. Please proceed.

DR. COEYTAUX: Thank you very much and thank you for the previous speakers. Dr. MacLeod and Dr. Fleg really provided an excellent background for what I'm about to present.

So I'm here to present and to summarize the reports of our draft technology assessment report entitled ECG-based Signal

Analysis Technologies for Evaluating Acute Coronary Syndrome.

As you mentioned, this report is presented and prepared by the Duke Evidence Based Practice Center and my name is Remy Coeytaux and Phil Leisy is here. Neither of us have any conflicts of interest related to this report.

Briefly, our team of investigators is multidisciplinary. I'm a family physician and a clinical epidemiologist. Dr. Sanders is an expert in systematic reviews.

Phil was very involved in this report as a summer intern with us. Dr. Wagner is an expert in electrophysiology and Dr. Green is a biostatistician.

Because the background was so well provided, I'll go over this fairly quickly, but I do want to, the overview of this presentation is I'll present a clinical context here with a background and then describe the key questions that we were tasked

to answer and then report on our methods, results and then give a few summary slides before questions and discussion.

The context of this is we focused primarily on the diagnosis and the work up of patients with acute coronary syndrome.

Now, the focus of the report includes patients who are either at intermediate or at low risk for coronary artery disease and I'll go into that in greater detail.

But I do want to take a moment to describe the term acute coronary syndrome. This term serves as a working diagnosis for patients presenting with symptoms suggestive of acute ischemic heart disease.

The acute coronary syndrome diagnosis is typically replaced by a more specific diagnosis as additional data become available in the course of evaluation of the patient.

The resting 12-lead

electrocardiogram, or ECG, is the first line test in working up patients with acute coronary syndrome.

There are essentially three possible test results from a standard ECG test in the setting of acute coronary syndrome.

One possibility is that there is evidence of ST-elevation myocardial infarction, or commonly known as STEMI, as well as a relatively new phenomenon of STEMI-equivalent, which is ST-depression, and you touched upon it a little bit before.

ST-depression in certain contexts is actually an ST-elevation depending on where in the location of the heart it is.

If there is ST-elevation occurring, if there's ischemia or infarct in the posterior part of the heart, it will show up as an ST-depression in the standard EKG.

And if you put leads in the back, as body surface mapping does, it would show up as an ST-elevation, so STEMI-equivalent is

considered equivalent to STEMI for our purposes and for clinical purposes. So that's one possibility of a test result from a EKG.

Another possibility is that there are signs that are suggestive of ischemia. You might have ST-depression. You may have dynamic T-wave inversion. This may suggest unstable angina or non-ST-elevation MI, otherwise known as NSTEMI, so that's a second possibility.

And the third possibility is that it's either, the test is normal or non-diagnostic. There may be some changes but really isn't pointing to a certain direction. So that's for the standard ECG.

Now the standard ECG is very, very important in the clinical work up of patients, but it has its limitations.

Among its limitations is as we previously reported that the ECG has low sensitivity for diagnosing ischemia or infarct.

And as Dr. MacLeod mentioned in response to one of the really pertinent questions, is it does not have a role for diagnosing coronary artery disease per se. It's not the test designed for that. It's not an anatomical test.

It's testing the electrical physiology and the electrical signals that are generated by the cells in the heart, and so it's not a test, per se, for coronary artery disease. The resting EKG is not.

And it does have low sensitivity for diagnosing ischemia or infarct, which is what it's largely used for, in addition to arrhythmias and other things. But the issue with this is that it does lead to a relatively high false negative rate.

This, in turn, leads to a not insignificant proportion of patients who are, in fact, experiencing ischemia or infarct but who may be misclassified as not having ischemic heart disease because of the false

negative.

And this has potentially important clinical outcomes. Poor clinical outcomes can be associated with withholding or delaying treatment for acute ischemic heart disease.

These inherent limitations of the resting 12-lead EKG has inspired the development of novel approaches for the detection of cardiac ischemia or infarct. Among these is what we're referring to as ECG-based signal analysis devices, or SAECG.

And these devices represent an emerging technology that process or interpret electrical signals generated by the heart in a way that is at least somewhat different from that of the standard 12-lead EKG.

Examples include mathematical analysis of ECG signals, high frequency QRS sampling, body surface mapping and vectorcardiography.

There is one last contextual issue that I'd like to raise and touch upon. The

clinical work up of any given patient should be informed by an assessment of the likelihood of that patient having a given clinical condition.

In the scenario of a diagnosing coronary artery disease, patients are commonly classified into one of three groups according to the likelihood of them having clinical manifestations of coronary artery disease.

These three groups are high-risk individuals, and these include patients with STEMI or STEMI-equivalent.

Second is intermediate-risk individuals which may include symptomatic patients with symptoms that are suggestive of ischemic heart disease.

And the third group is low risk and they may include asymptomatic individuals or patients who are symptomatic but whose likelihood of the symptoms being due to coronary artery disease is of lower likelihood.

So I mention this and I highlight this in the context of this report because our report in this presentation focuses on patients at intermediate or low risk for coronary artery disease.

And this is very important because we have in our report and in our systematic review of the literature, excluded studies that focus entirely on patients who had known STEMI at the time of presentation and that's an important point.

The key questions that we were tasked to answer are really in three parts. There are two key questions, but the first key question, key question 1, is in two parts.

The first part is what devices and methods for ECG-based signal analysis are used, or proposed to be used, for diagnosis of coronary artery disease and/or acute coronary syndrome in outpatient settings and in patients at low-to-intermediate risk, and what is the FDA status of these devices?

Key question 1b is what are considered the gold standard tests for the diagnosis of coronary artery disease and/or acute coronary syndrome in patients at low to intermediate risk and what are their strengths and limitations?

Key question 2 is in four parts. Question 2a, what is the evidence for the inter-rater, intra-rater, intra-patient and intra-device variability?

Question 2b, what is the evidence for diagnostic test performance compared to the reference standard used in the study? What factors affect test sensitivity and specificity?

2c is what is the evidence that ECG-based signal analysis technologies impact diagnostic decision-making?

And 2d, what is the evidence that ECG-based signal analysis technologies impact patient outcomes?

This slide illustrates our

analytic framework. The patient population, as I mentioned, are patients at low to intermediate risk for coronary artery disease or patients with symptoms suggestive of acute coronary syndrome.

Question 1a and Q1b address the technologies that are available for SAECG as well as, I'm talking about the criterion standards that can be used as comparators.

And outcomes have to do with the question Q2, key question 2, which really have to do with the various efficacies of this testing technology.

We followed standard procedure for conducting systematic reviews for this report. Each key question had a slightly different methodology.

Key question 1a, we relied primarily on the Gray literature to identify eligible devices, and you can see here some of the sources that we used to try to identify which devices that are out there to be

evaluated and have been used to evaluate patients with coronary artery disease and acute coronary syndrome.

Question Q1b was very well addressed by Dr. Fleg and it was really an assessment of the criterion standards for diagnosing on coronary artery disease, the test that can be used as a comparator for this new technology.

And we also looked at how the diagnosis of acute coronary syndrome is made and what criterion standards can be used for that.

And key question 2, our methods involved the standard systematic review procedures and we, on this, using the published literature, we synthesized the data and performed a meta-analysis.

Device and study eligibility criteria are as follows. One, a device had to be a physical device as opposed to a software device, for example, that obtains and

interprets information about the heart's electrical activity in ways that are different from the standard 12-lead ECG.

Two, a device had to be tested in adult patients at low to intermediate risk for coronary artery disease. Three, a device had to be available for purchase in the United States.

Four, it had to be readily implementable, and eligible studies had to report relevant outcomes including performance characteristics of the tests, effects of the tests on diagnostic or treatment decisions or effects on patient outcomes.

And finally, eligible studies had to have a sample size of at least 20 patients.

Our results, our Gray literature search identified 11 eligible devices, 6 of which are signal averaging devices, 1 is a body surface mapping device, 2 use mathematical analysis and 2 are vectorcardiograms.

Eight of the 11 devices have received FDA clearance, and I will leave this slide up for a few moments just for you to look at it.

Key question 1b was very, very well covered by Dr. Fleg. Our conclusions were identical to his.

In summary, therefore, I will go straight to the key points, which is coronary angiography is the gold standard for the diagnosis of coronary artery disease, and stress testing with imaging can be considered an acceptable criterion standard.

Imaging studies without exercise or pharmacological stress, the resting 12-lead EKG and stress testing with ECG are not acceptable as criterion standards for the diagnosis of coronary artery disease? Would you agree?

(No response)

DR. COEYTAUX: Okay. And that is generally, that's a good framework to work

with and is really what we work with in our report.

Biomarkers, we consider those to be incomplete reference standards. They do provide information on cardiac cell necrosis. In the clinical setting, elevated biomarkers are suggestive of myocardial infarction, but incomplete.

They, in and of themselves, are not satisfactory or acceptable as a complete criterion standard for the diagnosis of coronary artery disease.

Now, at the bottom of the slide, made a comment about acute coronary syndrome. There is no single criterion standard because acute coronary syndrome essentially is a working diagnosis.

It's pending further information so it's not quite the same as something else kind of, not trying to get to the diagnosis of acute coronary syndrome and have a test that tells you whether it is or not.

It's a little bit on the other, kind of reverse process. Patient comes in with symptoms suggestive of that and you replace that diagnosis with other more specific diagnosis as time go along, so there really is no criterion standard for that diagnosis.

The literature search results, we identified 1,957 titles and abstracts. We reviewed them and were left with 288 published studies that we read the full article to dig deeper down to see if they were, in fact, eligible.

And we ended up with 14 studies that were eligible, that met all our criteria. And those 14 studies represented 11 of the devices that, excuse me, there are 11 studies that are represented by 14 papers.

So there are 3 papers that duplicate studies but had new information, so 11 studies and 14 publications.

Key question 2a, this had to do

with the test performance inter-rater, reliability, et cetera, of test devices.

We only found a single study that provided pertinent data for this component of a key question. There was one study that looked at the PRIME ECG, which is a body surface mapping device.

And this study had two groups of readers. They had emergency physicians and emergency residents who were trained in the interpretation of the PRIME ECG.

They looked at their interpretation of the test results and they compared those interpretations with a group of experts in body surface mapping.

And there was reasonably good agreement and it appeared that, well, it didn't appear, but there was a tendency for emergency physicians to be more likely to interpret a study as negative than the body surface mapping experts in this study.

Key question 2b is really where

most of the results were found, where most of the evidence lies.

Eleven studies, 14 publications, were found. One of them was a good-quality study and ten were fair-quality studies. We used a standard method of assessing quality of studies.

There were several reasons why most of the studies didn't achieve good-quality status, but by and large it was the incomplete criterion standard.

Most of these studies used only biomarkers as the criterion standard and given that we had determined that that is not an acceptable and complete criterion standard, that, in and of itself, would bring a study down to fair quality.

And there were other reasons, but interesting enough that there were no poor-quality studies. All were observational cohort studies and they only represented two eligible devices.

So of the 11 devices that we had identified in the Gray literature search, only two are represented in the published literature that met our predetermined inclusion criteria, eligibility criteria for inclusion in this report.

One of the papers reported on the LP 3000 System, which is a signal analysis and signal averaging device. And the remainder evaluated the PRIME ECG, which is a body surface mapping device.

The one study that summarized the LP 3000 also compared, well, it compared the LP 3000 findings to coronary angiography.

So it was looking for coronary artery disease in patients who are symptomatic and we were able to estimate the sensitivity and specificity for that device.

And they also applied the standard ECG and so were able to estimate the sensitivity and specificity in that same population of the standard 12-lead ECG.

And the LP 3000, the sensitivity was 69 percent compared to 56 percent for the ECG and those differences were not statistically significant for this study, and the specificity was the same for both tests at 89 percent.

As I mentioned previously, 10 of the 11 studies evaluated the PRIME ECG body surface mapping device. Six of these studies were conducted in Ireland by the investigative team that originally developed the device.

Patients were recruited from emergency departments, cardiology wards and a mobile cardiology unit that was deployed to transport critically ill patients from the community to the hospital, so it was a much higher level than an ambulance, essentially a portable critical care unit.

Serum biomarkers were used as a criterion standard to diagnose myocardial infarction in these studies. And of note, the proprietary algorithm of the device is

evolving over time.

We conducted a meta-analysis of eight of the ten studies of the PRIME ECG. The results of this meta-analysis suggest that the sensitivity for the PRIME ECG for diagnosing acute MI is 68 percent compared to 41 percent for the 12-lead ECG.

The 95 percent confidence intervals for these two estimates overlap, so this finding from these data is not statistically significant.

Our estimates for the specificity for the PRIME ECG is 91 percent, compared to 95 percent for the 12-lead ECG. And positive and negative likelihood ratios were not significantly different between these two devices.

We did not identify any eligible studies that provided evidence for the impact of a signal analysis device on diagnostic decision-making.

And for key question 2d, we

identified two studies that provided pertinent information. The large OCCULT trial enrolled 1,830 patients including patients with STEMI.

The primary finding of this study as it relates to this particular key question is that ST-elevation detected by the PRIME ECG was associated with increased mortality, but this was not the case for ST-elevation detected by the standard ECG.

And the second study did collect post-discharge events data and they used this information to determine their sensitivity and specificity estimates, but they didn't report those data as far as outcomes so that we could use those.

So they collected data but didn't report it in a way that would be useful for us in terms of answering this question on patient outcomes.

So in summary, we found 11 studies represented by 14 publications that met our eligibility criteria. No eligible studies

included low-risk patients and none included patients that were asymptomatic.

Only two devices were evaluated in the target population and the meta-analysis that we performed suggests that the PRIME ECG may have higher sensitivity for detecting acute MI than the 12-lead ECG, 68 percent point estimate versus 41 percent.

But the 95 percent confidence intervals overlap and, therefore, this is not a statistically significant finding with these data.

And there is limited evidence that suggests that the PRIME ECG may provide early risk stratification information.

I think I emphasized the limited, there's limited evidence that suggests that PRIME ECG provided early risk stratification information. There is not information, we can't conclude either way.

As part of our process, we assessed the applicability of studies. And by

that, it is really kind of find a way to see how generalizable that the findings may be for studies.

It may be notable that six studies were conducted in Ireland and one was in England and one was in Greece.

And three studies were conducted in the U.S. and they included patients who appeared to us to represent the target population for the purpose of this report.

And we weren't sure whether or not that was as true for the studies conducted in Europe for a number of different reasons including this mobile cardiac care unit, which presumably has a different patient population than ours in the United States where we don't have these units, so we think that was worth noting.

And it is important to note that the PRIME ECG algorithm has evolved over time and that is by design.

They have a device that's been

working. They've been working on it for the last 12, 14 years, and the developers and the manufacturers are trying to fine tune it.

So that's not inherently a bad thing but it does make our job a little bit more challenging in that by looking over time, the device itself and the way it interprets data has changed over time.

And we did do a time series analysis not reported here to see if we could see if there were changes in the performance over time and we didn't detect that.

But it's worth noting that it's not a static test. It's a technology that is, even though it's been being developed over the last 20 or more years, it's still a bit of a moving target and that is something to be noted.

Future research needs, as we identified them, are that we believe there is a great need for studies with appropriate reference standards. That is one of the

biggest limitations of the existing literature.

The evaluation of existing ECG-based signal analysis devices, other than PRIME ECG, are lacking. Basically the literature, among the target population that we were interested in, is dominated by the PRIME ECG.

There really are no studies that we found that evaluate the impact of these devices on clinical decision-making and long-term patient outcomes, or very few. There was that one OCCULT trial.

And it would be probably useful to do an evaluation of patients in various subgroups including those who have suspected heart disease despite a non-diagnostic ECG. That could be an important niche for this additional information that's provided by these devices.

Other subgroups that might be relevant for study include conditions that

decrease the standard ECG's utility such as maybe left bundle branch block, specific age groups, maybe on people in another care population.

And by the way, all of these studies included patients above the age of 65. The median ranged from about 54 years to 68 years of age.

And studies that evaluate the utility of new devices in addition to, rather than instead of, a standard ECG.

The studies that we have here were ECG alongside a, done not simultaneously but concurrently in sequence with a new device.

And there are other designs that could be used to see what the utility is of the device in addition to instead of instead of the ECG.

And finally, and this is actually pretty important in the clinical setting, is that it would be helpful to have studies that compare test characteristics of new devices

with ECG, standard ECG, among patient populations that include STEMI and STEMI-equivalent.

In real life, patients come in, present and they represent the spectrum and we don't have the data here to really help us evaluate how these new devices perform with the whole spectrum of patients that present to us. Thank you.

DR. GOODMAN: Thank you very much, Dr. Coeytaux. Panel, let's do this. I know that we'll have several questions for Dr. Coeytaux and his team and I want to make sure that we're considering and asking those questions when we're comfortable.

So if you don't mind, let's take a ten-minute break now and we'll come back and ask some well-posed questions to Dr. Coeytaux.

So if you don't mind, we'll take our break now and if you'll return to the podium in about ten minutes we'll have some questions ginned up for you, okay?

DR. COEYTAUX: Very good, thank you.

DR. GOODMAN: Thank you. Let's take ten.

(Whereupon, the above-entitled matter went off the record at 10:04 a.m. and resumed at 10:17 a.m.)

DR. GOODMAN: Okay, we're going to reconvene now. Before the break, we heard the technology assessment presentation by Dr. Coeytaux.

And I know that we've got some scheduled public comments that we will certainly get to and we'll get to those in the time slot that ends by about 11 in the morning.

But having taken our quick bio-breaks here, I wanted to return to any questions that our panel has regarding the technology assessment.

I'm glad to report that the folks from Duke and ECU will be here for the balance

of the day, which means we can track them down later on if we need to.

Dr. Phurrough, did you have a question or two for starters here, sir?

DR. PHURROUGH: Yes, thank you. Steve Phurrough. I wanted to ask you about the technology assessment that you did in 2010 compared to the one that we see today.

In 2010, the questions were a bit different and there's a different volume of evidence that was reviewed and the conclusions are a bit different.

So are the differences in conclusions more related to the change in questions or are the conclusions different because there's a different volume of evidence or both?

DR. COEYTAUX: Yes, so we conducted a similar report a year ago, submitted it a year ago on this technology.

But then we were asked by CMS to not exactly revise it but to have an updated

report. The one that we submitted in 2010 had a different focus in terms of patient population.

DR. GOODMAN: Excuse me, I'm sorry. We're getting some loud, bad feedback on maybe an extra mic.

I wonder, Dr. Leisy, if you're maybe too close to that mic or if our technical person could make sure we don't have the disruptive feedback. I'm sorry to interrupt. Please continue.

DR. COEYTAUX: Not at all. I was noticing that as well. Is this better?

DR. GOODMAN: We hope so. Keep talking.

DR. COEYTAUX: Okay. So the report that we did and submitted a year ago was, there was very little literature then.

And so we were asked to looked at the SAECG technology without the focus on low- to intermediate-risk patient populations, so we had a broader spectrum of patients.

And as a result, we included studies that used another device that is not reported in this report, 3DMP is the name of one of those devices, that had good studies that were done in the laboratory in the coronary angiography suite where they induced ischemia.

And Dr. MacLeod actually showed one of that type of study that was done. That provides very good information about what information is provided by these devices when there is clearly ischemia, because they were able to induce ischemia in a very controlled manner.

Those are, I believe, four such studies that were included in the previous report that were pretty clearly not eligible and not included in this report because we were focusing only on low- to intermediate-risk patients for coronary artery disease.

And we made the judgment call that

patients who had found their way to coronary angiography and were having a procedure done were not, by and large, in the low- to intermediate-risk population.

So therein lies the greatest difference between the previous report and this report, so this report doesn't have that device. It doesn't have that patient population. It doesn't have that analysis.

And that is the primary if not the only reason, well, it's the primary reason for a slightly different conclusion.

The other important difference is the OCCULT trial, which is a very large and important trial which was published more recently, is included in this report and was only touched upon in the discussion of our previous report because it was published after the search had been conducted. Does that answer your question?

DR. PHURROUGH: Yes, thank you.

DR. GOODMAN: Thank you. And the

OCCULT trial was the one with the 1,830 patients, the largest sample size?

DR. COEYTAUX: That is correct, a multi-site study that was conducted in many sites including most of the United States but also in Ireland and in Canada, has a large sample size and also included both STEMI patients and patients who didn't have STEMI at presentation.

And the reason we were able to include this trial is because they separated the results. They provided results for both patient populations and allowed us to, therefore, present the results that we needed for the patients who didn't have STEMI.

And so, in summary, we excluded some studies in this study, in this report, because of the change in the focus of patient population and we included a new large study, the OCCULT trial, in this new one.

DR. GOODMAN: Great, thank you. Other questions, let's go in order. Dr.

McDonough was first, I believe.

DR. MCDONOUGH: Yes, just a quick clarification. When you were selecting, one of the questions were asked is about coronary artery disease in asymptomatic patients. That's not something that you were tasked to look at.

I think you were pretty clear. You were only looking at people who are symptomatic in terms of studies?

DR. COEYTAUX: I'm really sorry. There's one critical sentence that I didn't catch. Can you repeat that, please?

DR. MCDONOUGH: Yes. When I'm looking at your report and I'm looking at how you selected studies, you were looking for studies of patients who, among other characteristics, were symptomatic.

And the reason, the question I have is were you looking at all for asymptomatic patients?

And the reason I'm asking that

question is because one of the questions we, this committee, is being asked about is the ability of these tests to detect coronary artery disease in asymptomatic patients.

DR. COEYTAUX: Yes.

DR. MCDONOUGH: And that's not something that you looked at, right?

DR. COEYTAUX: I understand the question and it's a very pertinent question, very important. There's a two-part answer to this.

We did not exclude studies, I can say definitively that we did not exclude studies because of patients being asymptomatic.

Our search strategy, our MEDLINE searches, our librarian search, the collection of titles and abstracts for us to review was designed to not exclude patients who were asymptomatic.

So to the extent to which we've designed a good literature search strategy, we

think we did a good job, we would not have excluded those.

But there's a second stage to the process, which is the human element where two investigators independently review the titles and abstracts and make a judgment call for inclusion or exclusion.

In that process, it is possible that we would have missed studies for that reason. I'm certain that we at no point in the process actively excluded patients because they were asymptomatic.

But it is possible that in the cognitive process of investigators looking at the abstracts, and if there was any evidence that it might be eligible we'd go to the full text review, we may have missed those. I don't think we did.

I actually don't think these studies exist in the population of low to intermediate risk, in large part because of what Dr. MacLeod was saying, that these tests

are designed to detect events that are occurring at that time that have to do only when there is ischemia.

And so patients who are not, there probably aren't studies that are being done on asymptomatic patients under this device. Now, I could be wrong.

And I think part of the process of this MEDCAC process is if we in our job have missed those studies and anybody knows about them it's an opportunity for us to find out. But I don't think they're there and we did not exclude studies on that basis.

DR. GOODMAN: So just to clarify Dr. McDonough's, for my purposes anyway, his question, you did specifically seek studies on low to intermediate risk, low risk, and low risk would not have excluded asymptomatic patients at some risk of disease?

DR. COEYTAUX: That is correct.

DR. GOODMAN: Okay. However, in a subsequent step, through the human element in

sorting through studies, it's possible, though it sounds unlikely, it's possible that a study on asymptomatic patients could have been set aside?

DR. COEYTAUX: That is my assessment as well, yes.

DR. GOODMAN: Okay. Bob, does that answer your question?

DR. COEYTAUX: And I'd like Phil to respond to that as well.

DR. GOODMAN: Mr. Leisy.

MR. LEISY: Sure. So in our Gray literature search, we had a much different search criteria for devices in which we looked at any device that was used to detect myocardial ischemia regardless of presentation of the patient.

And it even included devices that were used for arrhythmia detection, which we have determined.

There are some devices that are used for both arrhythmia detection and

coronary artery disease detection or acute coronary syndrome and so we included these devices in our MEDLINE search independently.

And so if there was a device out there in the Gray literature that was used at some point to detect acute coronary syndrome or myocardial ischemia, it was included in the MEDLINE search and so those studies should have been populated in our MEDLINE search.

And then in our MEDLINE search criteria, we did not exclude asymptomatic patients and so we would have seen these studies if they were out there. Is that okay?

DR. GOODMAN: Okay. All right, thank you. Dr. McDonough, that suffices?

(No response)

DR. GOODMAN: Okay, just a moment. We'll go Samson, Steinbrook, Janowitz and then I think Heseltine, okay? Mr. Samson.

MR. SAMSON: Okay, I think to follow up on Bob McDonough's point, you do state in your Methods section in

inclusion/exclusion criteria, "The device must be tested in patients at low to intermediate risk for CAD who have a clinical presentation consistent with ACS."

That's a pretty clear statement that you were looking for symptomatic patients, and I think that for clarity purposes, you ought to revise that to make it more inclusive because it does give the message that you were only going to look for symptomatic patients.

The other point I wanted to raise was it's sort of implicit within the technology assessment that the role for SAECG is as an add on.

The fact that you're limiting the scope of it to low- and intermediate-risk patients, you're not focusing on high-risk patients, that in and of itself suggests that it's to be used as an add on to standard ECG.

Is that your thinking, that at least from the investigator's point of view

that that is the intended role of the test?

MR. LEISY: So while we did not draw that conclusion initially, practically how this technology is being used is as an adjunct as most patients that present to any outpatient facility having some sort of symptoms of either ischemia or coronary syndrome is going to get the standard 12-lead EKG.

And so most of our patient populations had that already on board and they just reported that data.

MR. SAMSON: I'm curious if any investigators are proposing that SAECG be used as a replacement for standard ECG.

DR. GOODMAN: Please speak closer to the mic, those of you at the podium.

DR. COEYTAUX: The question being did we find evidence that there are investigators who are proposing to use these devices as something other than adjunct?

We did read a number of editorials

and I'm thinking through to see if that has been proposed and I think yes.

I think that that was in the scope of what people are thinking about what this technology might be useful for, but I can't say for sure. I'm sorry.

DR. GOODMAN: Okay. Thanks, Mr. Samson. Dr. Steinbrook.

DR. STEINBROOK: Thank you. I wanted to draw you out a bit to elaborate on the issue with the PRIME ECG of the so-called limited evidence of patients with ST-elevation detected by the PRIME ECG having increased mortality as compared to that not being the case when ST-elevation was determined with the 12-lead ECG.

I'm looking at Page 39 of your technology assessment and I noticed in looking back at that that the odds ratio associated with this finding increased mortality was 11.2 but the confidence intervals, shall we say, were rather wide, from 1.8 to 67.

Now, I can't do the math in my head to back calculate what the differences were, what the actual numbers were.

But could you explain this some more and tell us whether limited is the right word or inconclusive is the right word and also your two competing explanations of why this may be the case?

DR. COEYTAUX: If I may, I know where that information is. I'll go right now and look at the original article if we may ask the next question while I go and get that and in a minute or two come back with the article in front of me. May I do that?

DR. STEINBROOK: Sure.

DR. COEYTAUX: Great, thank you.

DR. GOODMAN: Okay, yes, go ahead. Dr. Janowitz I think was next.

DR. JANOWITZ: I had the same question so.

DR. GOODMAN: Okay. Dr. Heseltine.

DR. HESELTINE: So I'd like to sort of turn this question around slightly.

If you agree that there are special populations within the acute coronary syndrome group who may not, in fact, show coronary angiography evidence of atheroma but in fact have small vessel disease, were these people targeted or viewed or reviewed in your technology assessment?

MR. LEISY: So these patients with microvascular disease, if that's okay, we'll call it that.

DR. GOODMAN: Closer to the microphone, please.

MR. LEISY: Sorry. These patients with microvascular disease, as we'll call them, were not excluded.

And the technology is pretty beneficial in the body surface mapping because that is designed to detect ischemia in areas that are not already detected in the 12-lead ECG.

So that sort of technology is there in use. I think that is part of the argument for using that technology.

Now, the other technologies that are out there that only use either standard ECG, that only detect really the three major coronary vessels, may not be as sufficient in detection of that.

But these studies did not comment on whether or not it was beneficial in either microvascular versus the, we'll say, macrovascular of the major coronary vessels.

DR. GOODMAN: Is that a satisfactory answer, Dr. Heseltine?

DR. HESELTINE: Yes.

DR. GOODMAN: Okay, thank you. Dr. Saadi's next.

DR. SAADI: So my question is about your meta-analysis. So on your meta-analysis, you had mentioned I think during your presentation that this, can you hear me all right?

MR. LEISY: A little bit louder if you don't mind.

DR. SAADI: Okay, so you actually had mentioned that is study, right? So the meta-analysis that combines the data from a wide, sort of in a time frame.

This actually I heard first in my personal, you know, experiment, that what actually you have seen is that there's an underlying mathematical problem which is working, right, to make these products work.

So my question is sort of like in a twofold. One is how confident are you in terms of combining and putting all this data in one bucket? I think you mentioned in terms of, you know, heterogenicity and things like that.

Would you actually say that it is fair to make assessment and draw conclusion based on sort of like in data points which might not be actually, you cannot probably combine them scientifically. So that's

actually question number one.

And the second question is that you have mentioned only two products, right, so the PRIME and LP 3000. So what's the part about the other product?

Where's the part about the other product? Is that because actually they don't have the data or you don't actually have access to any of this data? You mentioned that there are some, you know, limitations in terms of the access.

DR. GOODMAN: So which question are we answering now, Dr. Saadi's or Dr. Steinbrook's?

DR. COEYTAUX: Dr. Steinbrook's.

DR. GOODMAN: Okay, let's return to Dr. Steinbrook's question then. Proceed.

DR. COEYTAUX: Yes, I'm sorry. Which would you prefer? We can do either.

DR. GOODMAN: Let's go with Steinbrook's while we get some, I see we're doing some homework on Dr. Saadi's. So if you

would help us, restate what you recall Dr. Steinbrook sought from you and give us an answer.

DR. COEYTAUX: Yes, and Dr. Steinbrook's is the one about the meta-analysis? I --

DR. GOODMAN: Dr. Steinbrook? No. Restate your question, Dr. Steinbrook. He had to go back and get a reference.

DR. COEYTAUX: Okay, I remember the question. It's actually Dr. Saadi's that I can answer right away while Phil is looking at that paragraph. I misspoke.

DR. GOODMAN: Oh, you confused me, okay.

DR. COEYTAUX: Yes, this --

DR. GOODMAN: So stop.

DR. COEYTAUX: Yes.

DR. GOODMAN: Going to answer Dr. Saadi's question about meta-analysis now?

DR. COEYTAUX: Yes, please.

DR. GOODMAN: Do proceed.

DR. COEYTAUX: Thank you. Two-part question as I understand. The first part of the question is how confident are we given the heterogeneity of the studies in doing a meta-analysis and being confident in the validity of our findings? Is that the correct question?

DR. SAADI: Yes.

DR. COEYTAUX: In this case, confident. We have a biostatistician who was very familiar with these types of analyses.

And she did many different, she looked at the data in many different ways to see if there were problems in the heterogeneity, that that would lead to an unstable estimate, and it doesn't look like it's the case.

The 8 studies that were included in the meta-analysis, I believe 6 of them had data from 1 group that were very consistent over 10 years, 10 or 12, 1998 I guess to 2010, in their collection of data.

They essentially had a series of patients with non-overlapping patient populations that they tested the PRIME ECG on.

And we did not find any evidence that there was a significant change over time, so we feel like that is a fairly robust group of patients that we can put together in a meta-analysis.

And furthermore, they were, that group was also involved in the OCCULT trial, which is the larger one that was weighted most heavily in the meta-analysis.

The OCCULT trial used a more appropriate criterion standard than the previous ones. Previous ones just used biomarkers to, that was the criterion standard for acute MI. The OCCULT study did more than that.

They used biomarkers but they had a study-adjudicated diagnosis at the end of myocardial infarction or not, so it was more complex. But we think that that is a

reasonable combining of outcome.

That's one of the problems with meta-analyses, that different settings may have different outcomes. But we feel like since the comparator, since the outcome of interest was MI, that we feel like that was an appropriate one.

So the short answer is, yes, I do believe the meta-analysis is as valid as can be for that particular analytical method.

DR. SAADI: Okay.

DR. GOODMAN: Dr. Saadi looks satisfied with that answer. Do you have a response yet for Dr. Steinbrook's question?

DR. COEYTAUX: One moment, please.

DR. GOODMAN: Pending. Dr. Steinbrook, would you mind restating your question in kind of a brief form?

DR. STEINBROOK: Okay, we're looking at the issue of risk stratification with the PRIME ECG device and the finding that if ST-elevation was detected by that device it

was associated with an increased mortality, odds ratio 11.2, confidence interval 1.8 to 67.

That was not the case, however, with standard 12-lead ECG.

DR. GOODMAN: And you had referred to a pretty wide confidence interval.

DR. STEINBROOK: Exactly, I was trying to get some more information about the numbers underlying that odds ratio result.

DR. GOODMAN: The TA team is conferring. And I'll just, while in this small period, we don't have people signed up to do public presentations, so that's giving us a little bit more time on our agenda.

That's why we're allowing this part of the agenda to go over a bit. We're saving some time at the other end.

MR. LEISY: So in the study that you are addressing about the OCCULT trial, the secondary analysis of the long-term patient outcome.

In their Discussion section, they mentioned that this was a subsequent finding, that patients who did not present with ST-elevation 12-lead and subsequent presented with STEMI on the 80-lead body surface map tended to have a higher mortality rate with the follow up of the trial.

In their Discussion section, they don't attribute that to any one risk factor or any explanation for that.

They discussed it as a subsequent finding and they admit that the trial was not set up to specifically detect that information.

I think it was something that they just came across. It was a pertinent finding. They decided to republish in a different report, but that was the discussion on the objective there.

DR. GOODMAN: Thank you.

MR. LEISY: You're welcome.

DR. GOODMAN: Dr. Steinbrook, you

okay with the response?

DR. STEINBROOK: Well, I guess, and this could even be perhaps brought back later after the break or later today.

But my concern was that even though the odds ratio itself is rather high, the confidence intervals are so wide that somehow the difference is the number events, there must be some small numbers there.

And so I'm trying to get at the issue as to whether one might consider this limited evidence or inconclusive evidence. They're similar but they're different.

I just was really struck by that wide confidence interval, and since this is relevant to the things we need to vote on later, I was just trying to get some more clarity on how we should view the findings.

DR. COEYTAUX: As the person who did that part of the report and decided to put in limited evidence, I should address that. I agree and I think it's a very good question.

My thinking as I was writing that is I felt that because in the key question there was a large, well-designed study that had data that pertained to outcomes, that I wanted to include that in the summary saying we have some data.

We don't have any data, and I wanted to bring that to the level of a conclusion. And my definition of limited, what I had in mind is we have some but it's not very much but at least it's some and it could be, it's not conclusive either way.

So I would like to get the terminology right and I think that the limited, the term limited is implying some things which, I even took a double take myself.

I remember as I was reading the presentation, I unintentionally accentuated limited evidence. I didn't really mean it that way.

There is evidence that has

uncertain validity in support of outcomes being affected by this test. In layman's terms, that's what I was thinking in writing those terms. Can you comment on that?

DR. GOODMAN: I think we got the point, right?

DR. STEINBROOK: Thank you. Thank you.

DR. GOODMAN: Okay.

DR. COEYTAUX: Okay, thank you.

DR. GOODMAN: Sometimes when there isn't a lot of rigorous evidence available, we still are in search of the best evidence and sometimes the best available evidence ain't so great.

DR. COEYTAUX: Yes.

DR. GOODMAN: Which is the technical term of what you're trying to say I'm sure. So Dr. Janowitz had a comment and then Mr. Samson, and let's keep these brief. We're going to move on pretty soon.

DR. JANOWITZ: Is there any data

concerning gender differences on this technique?

DR. COEYTAUX: I'm glad you asked that. No, and we weren't tasked to look for that but, very quickly, as part of our other reports that we're doing and projects, we have many cardiology projects that are looking at gender data.

So I was actually sensitized to look for that and I informally looked at that and, no, I didn't recall finding any and I did an informal look myself.

DR. GOODMAN: Thank you. Mr. Samson.

MR. SAMSON: Okay, in the meta-analysis, there was a high degree of statistical heterogeneity.

And typically it's the task of the people doing the meta-analysis to try to explore potential sources for that heterogeneity in the clinical or methodological heterogeneity that is present

in the evidence base.

And did you find any clues that might explain some of that heterogeneity, either in variations in patient populations or in the way the studies were done?

DR. COEYTAUX: Another good question. I can only myself, unfortunately, address the clinical. I'm a clinician and I'm trained in the critical appraisal of the literature. I'm not trained in meta-analysis techniques.

So the part of your question has to do with the biostatistician looking for clues to why there's heterogeneity. I don't know.

I know that she attended to that and we had discussions about, you know, are these, we had basically asked her the same questions that you had asked. Is it valid? And she said she thinks it is. So I can't really comment on that.

As far as the clinical one, this

seemed like a pretty homogeneous, clinically, group of studies and patients.

So I don't have great insights as to heterogeneity for these particular eight studies because they were as close together as I, as a clinician, tend to see in a group of studies which a meta-analysis is performed on, so I don't have insight to that.

MR. SAMSON: Perhaps it has to do with the evolving nature of the test itself.

DR. COEYTAUX: And that is potentially a very good explanation. That may well be.

We did ask our biostatistician to look at that specific question simply by doing, I think it was called a time series analysis where she looked at the six studies that were done in Ireland to see if she noticed a difference.

And she came back saying, no, she didn't see that, but maybe there's still heterogeneity involved in that from that. I

really don't know so that --

MR. SAMSON: Okay. One more, I'm sorry, one more quick question.

DR. GOODMAN: Briefly.

MR. SAMSON: Yes, you have a diagram at the beginning of the Results chapter about the flow of the screening of the results and you identified 58 studies that were excluded for not being in the target population.

I was wondering if you could just characterize the mix of those 58 studies. Were they primarily high risk?

Were they perhaps patients suspected of having arrhythmias, you know, maybe treatment monitoring? What can you say about that?

DR. COEYTAUX: I'm certain that a proportion of them were high risk. I know of many of the studies that were in patients who were already like in the cath lab. So that is certainly a proportion.

We went back after the fact, based on some of the discussion, to see if maybe there were, the asymptomatic question. We went back to see if we had maybe missed something.

So we went to that group of studies to see if we had excluded for asymptomatic reasons and we did not, so that's not the group of patients that's in there.

So I think probably it's mostly the high risk and focusing on arrhythmias. Phil, would you agree?

MR. LEISY: I agree. A great number of the ones that were excluded for not our target population were because they were for arrhythmia detection and not ischemia or coronary artery disease detection.

A great number of them were for that reason. The other ones did either include STEMI population or were the high-risk group.

DR. GOODMAN: Good, thank you.

This is our last question for this segment. Dr. McDonough, did you have a closing for this section?

DR. MCDONOUGH: Yes, well, so many of the studies the PRIME ECG used cardiac biomarkers as a reference standard.

And I guess part of the reason you're concluding it's incomplete is because myocardial necrosis is only sort of a subset of ischemia.

But is it also sort of implicit, sort of a judgment about the value of a test that would use another test which is relatively easy to perform and inexpensive as a reference standard? You understand what I'm saying?

In other words, it's easy to get cardiac biomarkers. Why would you, to get evidence of myocardial necrosis, so what's the value of having yet another test to do that?

DR. COEYTAUX: Yes. I hope we didn't apply that bias ourselves, I don't

know, in terms of being biased against a simple test.

Our thinking in that, and it wasn't just our thinking. We really reviewed the literature as part of one of the key questions to see what's in use and what are the rationales for these different tests.

But it is mainly for what you mentioned earlier. It's a subset. Only patients who have necrosis, I believe. That's my understanding and please correct me if I'm wrong.

But only patients who have cardiac necrosis or the MB fraction but basically muscular cell death are going to have detectable out-of-range levels of biomarkers in the blood, at least for the CK-MBs.

And troponin being sensitive, but also being nonspecific that we feel like that is not, for diagnosing coronary artery disease, it is not an appropriate test because it's really just looking at the manifestations

of it.

So that's the other reason, is that coronary artery disease is an anatomical problem which is lesions in the coronary artery disease of which serum biomarkers is hinting at manifestations of acute problems most likely due to that.

That was our thinking and not really meaning to have a bias towards another simple test.

DR. GOODMAN: Thank you.

DR. COEYTAUX: Is that satisfactory?

DR. MCDONOUGH: Yes.

DR. GOODMAN: Yes. I think that makes sense and is consistent with other things we've seen in the literature.

Okay, we're going to move on now to our speaker list. There are four. So our TA folks from the EPC are going to be around for the rest of the day, so we will have further opportunity to ask them questions so

that was not our last opportunity.

We're going to have four times, seven minutes per speaker now, and our first speaker is Dr. Joseph Shen, who's an MCG technology developer, Founder and Managing Member of Premier Heart, LLC. Welcome, Dr. Shen.

DR. SHEN: Thank you. My name is Joseph Shen. It's my pleasure to present MCG, Multifunction CardioGram. I'm also the developer and founder of the company. Here my purpose of talk is to talk about how MCG works.

MCG is entirely different than 12-lead ECG, a resting or a stress ECG, in that matter. MCG focus on systems theory using the, study the communication between different parts of a system.

And the system analysis actually is to, we dissect the system into different components, study it and then put the systems back into a whole then to hopefully still have

better understanding of the system. The system we're talking about is human heart.

The traditional ECG, as we have heard from many speakers, is focusing on one cycle of one lead at a time and the segments of that particular cycle, such as the QRS complex, ST segments, et cetera, and then the information has to be interpreted, integrated by an expert.

MCG is entirely different. MCG is studying the relationship between two resting lead over multiple cycles and converting the information, dissect the information, do multiple mathematical functions by extracting information from a large empirical database to study the dynamic changes over multiple cycles.

What is the mathematics and physics behind this? Simply said, when the blood flows through the heart, it interacts with the myocardium and as that happens you have dynamic changes and stress and strain

caused by the interaction.

Mathematically speaking, the theoretical model is based on LaGrange-Euler complex. LaGrange is description of the myocardium muscles, and Euler is description of the blood property.

And Laplace Transformation was the key to link these two together and make them into one complex.

The application side of the theory is the development of the Multifunction CardioGram by using six different functions to dissect the system, then extract the information, 166 indices developed over the years to study the heart as a whole.

Here is the six functions. Anybody interested can come and we'll talk more.

Here's how the data is collected. You have a patient at rest, supine, in a physician's office and then 82 seconds worth of data collected from 2-lead resting ECG.

Then the information amplified, digitized, encrypted, transmitted through the Internet to a data center.

On the data center side, the information then is decrypted, then the discrete fourier transformation is applied.

Then a series of digital signal processing to clean up the signal, then mathematical transformations, then the identification of the index clusters, then pattern matching of the 40,000-patient database is used as foundation for detection of ischemia or coronary obstruct.

The report will come back with a score from 0 to 20 and then the detection of a local or global ischemia may lead to a report to the physician so if it is a critical stenosis, severity of coronary artery disease.

The report needs to report back to a physician. The whole process takes about five minutes. Obviously, the database is the most important part of this.

Over the years, we have accumulated 40,000 people in the database out of 100,000 candidates and 60 percent were excluded because due to the best quality of data or incompleteness or redundancy in the data.

However, the data existing had 1/3 patient population are completely normal people and age range from 14 to 100 years old with equal size male and female.

For the disease side, is the same. You have 50 percent male and 50 percent female, age group from 14 to 100 and with variety of pathologies.

The pathology, the patient clinical data had to be verified by two independent experts in the field and a third sometimes had to be used to break the impasse.

And the reason we said there's no bias introduced because we used a normalization process of age and sex for both the normal group and the disease group to make

sure that bias is eliminated.

The data also include patient's sex, age, risk factors, medical history, results of MCG, the index clusters and also if there's angiography and other noninvasive testing used for objective assessment of patient medical condition.

And, again, as I said, 50 percent of the people in the database are women and that's the reason why perhaps MCG can provide equal accuracy for men and women in the same age group. The age range, again, from 14 to 100.

Again, I will not, due to time constraints, I have one minute left. Basically the other factor that I believe is important is looking at the variety of disease entities.

Pure heart disease or coronary disease with other conditions or other conditions without coronary disease, a variety of degree of a coronary disease from as little

as 30, 40 percent to 100 percent.

Then the other part is that, I don't know why this is happening, okay. Right side is the 12-lead ECG. You have a handful of indices to study.

The right side is one of the six functions of MCG. Has 25 more indices. Over here is 166. So much more information can be extracted from MCG.

And here is an example. Bottom is a normal person with no coronary disease and the left side is patient pre-stent with coronary disease and the right side is immediate post-stent with some recovery.

And, again, I want to say is that the ECG versus MCG, ECG has subjectivity introduced due to dependent on expert reading. MCG is completely automatic, 100 percent objective and based on an empirical database.

Lastly, we use mathematics theory, empirical data and clinical validation to build the system to detect ischemia

effectively with high sensitivity/specificity. Thank you.

DR. GOODMAN: Thank you very much, Dr. Shen. It's been at least a few days since I've had to face up to a Laplace Transformation or non-Newtonian fluid dynamics.

So we appreciate the refresher course, although the latter's important, I think, in artificial hearts as it turns out.

DR. SHEN: I'm sorry?

DR. GOODMAN: That was my bad attempt at being humorous. Okay, thank you very much and I hope you'll be around for much of the rest of the day.

Dr. Michael Imhoff is next. Dr. Imhoff comes from the Ruhr-University in Bochum, Germany. Welcome, Dr. Imhoff.

DR. IMHOFF: Thank you very much, folks, for having me there. First a few disclosures, my wife owns a minor share, less than one percent, of Premier Heart.

My travel was paid by Premier Heart. But no other party took any influence on the presentation that I'm here to give and it's all based on peer review and already published studies.

I would like to talk briefly about some validation studies including more than 1,000 patients scheduled for coronary angiography done with MCG.

MCG results were compared to angiography. The MCG was done prior to angiography. Therefore, any influence of any intervention during the angiography could be ruled out.

So there is maybe a slight misperception. MCG was not tested in patients with induced ischemia but in a consecutive population of patients scheduled for coronary angiography.

The angiograms were verified by two angiographers independently, and for MCG and the angiographies the design was always

double-blind. We included patients of, there were three major studies in Westchester in the U.S., in Siegburg in Germany and in Asia, a multi-center trial including four sites. The Siegburg trial and the Asian trial explicitly excluded patients with ACS or AMI.

The severity score, which is one of the core parameters of MCG, is an assessment of the probability of having relevant coronary stenosis, and the higher the score, the more probable coronary stenosis is.

And if we look at the entire population of 1,076 patients, we see that those patients who have the relevant stenosis in the angiogram also have a significantly higher severity score.

And there's relatively little overlap between patients that do not have stenosis and those who have stenosis.

And if we do a subgroup analysis, here for example gender and age group, we see that these differences are maintained

throughout different subgroups.

If we take a cutoff of 4 for defining patients with a probable coronary stenosis, we see that patients that have a score of less than 4 predominantly do not have stenosis in angiography and patients who have a score of 4 or higher predominantly have stenosis.

And if we look now at the more detailed data, we have an a priori pre-test probability. So the prevalence of coronary stenosis in our patients was about 43 percent, of which nearly 88 percent are correctly classified as having stenosis or no stenosis.

We have a sensitivity of 90 percent. We have specificity of 85 percent.

If you look at subgroups, for instance here gender, age groups, all of the patients prior to inclusion in the study had any kind of revascularization, we see that the diagnostic performance for sensitivity and for specificity does not differ markedly between

these different subgroups.

And we have a negative predictive value which is maintained over 90 percent for the entire population and for our subgroups that we investigated.

No surprises here. If we look at the receiver operating characteristic curves, we see that for all patients we have nearly, another curve of nearly .9.

And if we look at different subgroups here, the different study centers also represent different clinical practice, different gender, age groups and, again, revascularization status.

So we see that the ROC curves are pretty close together, indicating that the diagnostic performance in the different subgroups is very similar.

Of course, the studies have their limitations. As the studies have very similar study designs, these limitations apply to all the studies.

They are convenient samples but on the other hand, they are, from a demographic perspective, a good match to the typical CAD populations.

We have a prevalence of CAD of less than 50 percent, therefore, as a group and also the subgroups, these patients qualify as intermediate risk.

There are no high-risk patients included in these studies, especially not in the Asian and the German studies.

We used as a reference standard the coronary angiography, which is the accepted gold standard but, as we learned, it's a morphologic standard.

Therefore, as MCG is a functional diagnostic means, it may underestimate the actual, the true MCG sensitivity and specificity.

There was, of course, bias introduced because all these patients were already scheduled for coronary angiography

but, again, with a close match to the typical CAD population.

And we compared also the data to those of the ACC's registry but excluding ACS patients but it's also a very good match to that data.

There's, of course, by study design, one shortcoming. We did not do a direct comparison to any other stress test modality.

So let me briefly summarize. We looked at the computerized resting ECG analysis, the MCG methodology in 1,076 patients.

We found in comparison to coronary angiography 88 percent correct predictions of whether or not coronary stenosis was present, with a sensitivity of 91 percent and a specificity of 85 percent, a negative predictive value of over 90 percent.

And we did not find in any of those studies a significant effect on the

diagnostic performance of MCG from different gender, age, revascularization status or study location.

And again, these patients did not have induced ischemia. There were no ACS or AMI patients included and statistically speaking they may represent an intermediate-risk population. Thank you very much.

DR. GOODMAN: Thank you, Dr. Imhoff. Dr. Imhoff, just stay at the podium for a moment, please.

Just for clarification purposes for our panel, Dr. Imhoff's slides were included in this binder of presentations.

Although he was the second speaker, it's the third one shown so that's for further reference. Make sure you did have that.

Second, Dr. Imhoff, I just want to make sure I understand and I apologize if I don't. Your device is the same as the one

listed in the technology assessment that is identified as the 3DMP MCG and --

DR. IMHOFF: Correct.

DR. GOODMAN: -- by Premier Heart. That's the same one.

DR. IMHOFF: Correct, that's the same device.

DR. GOODMAN: Thank you.

DR. IMHOFF: And between those studies, the algorithms used in the device were not changed while the name was changed.

DR. GOODMAN: Okay, that helps. And if I'm not mistaken then, when our TA people found 11 studies for which there are 14 articles, 1 was for the LP 3000, 10 were for the PRIME ECG but they found none on your technology. There's not something in the literature that's relevant.

DR. IMHOFF: Well, my understanding is that they found the publications but these publications were excluded because they did not fit the

inclusion criteria.

DR. GOODMAN: Right.

DR. IMHOFF: But I'm a little bit surprised about that because if one of the exclusion criteria was induced ischemia, this is not valid.

DR. GOODMAN: Okay, so that's where I saw a disconnect and I think we may come to that later on. I just wanted to put a bookmark on it now. Thank you very much, Dr. Imhoff. That was very helpful. Okay, thank you.

Our next presenter is Dr. John Strobeck from Heart-Lung Associates in Hawthorne, New Jersey. Welcome, Dr. Strobeck.

DR. STROBECK: Thank you very much, it's a tremendous pleasure to able to present some information to you on multifunction cardiography. As I said, I'm John Strobeck and I'm a practicing cardiologist in northern New Jersey. And I'm here to talk to you about the multifunction

cardiogram. I have no disclosures.

I'm going to talk about, or at least review some of the information on the state of the art. Coronary disease detection. We're going to talk a little but more about unmet needs of noninvasive diagnostic tests currently applied. Particularly in women.

And I'm going to talk about the direct comparison data of MCG to SPECT Myocardial Profusion Imaging which was recently published.

This article which I think has been tremendously helpful for us in terms of focusing our attention. Was published in March of 2010 dealing with the findings of Manesh Patel and the group at Duke. Of the absolutely, I thought surprisingly low yield of elective coronary angiography in this country.

This study, for many of you who haven't seen it was a retrospective study, it included 400,000 patients without known

coronary artery disease who undergoing elective catheterization.

Obviously people that have acute coronary syndromes, or high risk types of problems were excluded.

The relevant stenosis defined in this trial as being positive was a 70 percent stenosis, not a 50 percent stenosis of a major epicardial vessel. But the 50 percent stenosis threshold was maintained for the left main disease.

This study group, in our view, was very similar to the study groups that we involved in over 1,000 patients using MCG technology. At least in terms of demographics.

The findings were significant, only 38 percent of patients who get to coronary angiography as a result of all of our sequential noninvasive tests that are currently being used. Only 38 percent had stenosis greater than 70 percent. A full 39

percent had normal exams.

In the female cohort, only 33 percent had relevant stenosis suggesting that we're studying, or least submitting to angiography a lot of women that don't need it.

Of the 400,000 patients a full 84 percent had tested positive on sequential noninvasive testing. But that could have meant an EKG, it could have meant an exercise or pharmacological stress test using either radionuclide or ECHO Imaging technology.

But only 41 percent of this 84 percent really had obstructive disease.

In conclusion, although there were some limitations to this study the Patel study showed, I think alarmingly that most of us in community-based practices are not catheterizating a very high percentage of people who have obstructive coronary disease.

We need new technology obviously to help us and support out efforts to really send for invasive strategies the people who

need it.

Currently SPECT Myocardial Perfusion Imaging is the test of choice, or at least, a highly used test. To detect myocardial ischemia under stress conditions, and then that data is used to refer patients for cardiac catheterizating.

There's a long list of limitations for this test, poor spatial resolution, difficulties when there's a arrhythmia, and also the well noted attenuation defects are important to take into account.

A couple of recent studies of meta-analyses have been done that demonstrate what seems to be decent sensitivity and specificity in patients undergoing SPECT profusion imaging. But I want you to note that both of these meta-analyses used a 50 percent stenosis as the threshold for assigning true positivity or true negativity.

And a 75 percent prevalence of coronary disease in the population studies.

So these were in my view, much higher risk populations. And as we all know, sensitivity and specificity increase significantly for any diagnostic test when the higher risk populations are bing studied.

I want to talk a little bit about women. Women obviously have major issues relative to cardiovascular disease. More deaths in women per year than in men.

In patients who have a myocardial infarction the mortality within the first year after myocardial infarction is higher in women in all age groups.

This segment of the population deserves significant assistance in terms of either dealing with under recognized disease and more effective, utilization, application of our current resources.

This is the trial that was just recently published, it is a paired comparison trial of multifunction cardiograms to SPECT Myocardial Perfusion Imaging in a community-

based setting.

A single center study of a 116 consecutive patients that were referred for evaluation and symptoms suggestive of coronary artery disease.

DR. GOODMAN: Dr. Strobeck, can you finish in one minute please?

DR. STROBECK: Yes. This study showed that when MCG was compared with Nuclear stress testing that the sensitivity and specificity for MCG was considerably higher than for nuclear stress testing.

That sensitivity and specificity difference persisted for females and when accuracy was looked at the accuracy of MCG compared to the accuracy of stress profusion imaging was considerable different.

MCG was considerable more accurate. And this number 89 percent has appeared routinely in all the clinical trials. Female accuracy was identical.

I want to talk a little bit about

the important questions.

DR. GOODMAN: It will have to be a little bit, please make your final point, sir.

DR. STROBECK: Okay. We think that MCG supports a positive or a yes vote for these specific questions, 1b, 2b, 3b, Questions, 4b, 5c and 6c.

We are quite confident that these generalizations are, that our findings are generalizable to the medicare population as well as community-based settings.

Some of the other questions in particular Question Number 7 and Number 8 we think require some further discussion, although health care outcomes, particularly related to angiography outcomes are considerably improved if MCG is used as the bases for referral for coronary angiography.

DR. GOODMAN: Dr. Strobeck, you have to finish now, thank you very much and we need to go on to our next speaker. I appreciate your insights. Thank you, sir.

DR. STROBECK: Thank you, very much.

DR. GOODMAN: Just a kind suggestion for next time, you might want to consider fewer than 30 slides for a seven minute time slot. A lot of what you said was very useful but we want to get to the best of it next time. Thank you, sir.

Our next speaker is Dr. Amir Beker, he's chairman of BSP, Biological Signal Precessing Inc. Welcome Dr. Beker.

DR. BEKER: Thank you very much. And I thank members of the committee for the opportunity to appear here and present evidence and comments regarding the High-Frequency QRS analysis technology. I am the founder and chairman of BSP biological signal processing.

BSP is a developer and maker of computerized systems for the diagnosis and monitoring of ischemia heart disease. Cleared by the FDA that are based on high frequency

QRS analysis.

I'll do my best to concluded my nine slide presentation in less than seven minutes and assist the committee with timing issues.

DR. GOODMAN: Take the full seven, sir. Take the full seven.

DR. BEKER: Okay. Next slide please.

DR. GOODMAN: I think you're in control.

DR. BEKER: Yes, I have it, good. Analysis of ST changes during exercise testing has been used for decades as first line test for coronary artery disease in spite of the vast agreement that the performance of commonly accepted clinical tool is limited by low sensitivity and specificity.

Clinical accuracy values reported for women are particularly low. Making women an under served population in terms of initial diagnosis for ischemic heart disease.

Main implications of stress test low clinical accuracy include unnecessary radioactive and invasive follow-up tests. High percentage of false negative cases and excessive costs to the health system.

High frequency QRS in a complex analysis, or in its commercial name HyperQ, is based on quantitative analysis of fast-varying low amplitude wave components. The high frequency components that are part of the QRS portion of the ECG signal.

High frequency QRS analysis is not a signal averaging technology, rather it is a technology that captures and analyzes the high frequency components of the ECG signal during the depolarization phase.

Components that are highly sensitive and specific to ischemic conditions of the myocardium as numerous basic science experiments and clinical studies have demonstrated since the early 1980's.

By the way, the changes in high

frequency components during these scanning conditions has much to do with the changes in the action potential as shown by Dr. MacLeod earlier. And with the presentation of the activation waveforms.

And already available clinical implementation of the High-Frequency QRS technology is the FDA cleared stress high-frequency system for the detection of coronary artery disease.

Please note that the high frequency analysis is used as an aid to the ECG stress test. In conjunction with and as a part of clinical stress test. And not instead of stress testing.

One of the two examples I have here for a study demonstrating the clinical value of High-Frequency QRS technology is this one.

This study was excepted for publication in the American Journal of Cardiology after this presentation was

submitted to the committee organizer. So the reference there should be in press, or accepted.

The study included 941 consecutive patients referred to SPECT cardiac nuclear imaging for evaluation of coronary artery disease.

All patients underwent stress ECG, stress HyperQ tests and cardiac nuclear imaging. Results and conclusions of the study HyperQ index offered significant improvement of the diagnostic value over clinic exercise tests.

Linking it to the questions discussed today, higher diagnostic value improves physician decision making. Especially in inconclusive and non-diagnostic populations. Improves patient outcomes and reduces the rate of unnecessary radioactive and invasive procedures.

A ST segment analysis high frequency QRS analysis has shown gender

independence sensitivity and specificity and marked improvement of clinical accuracy in women.

Following is a summary of the study in women population where the reference standard used was angiography for all enrolled patients. Again the results demonstrated significantly improved clinical accuracy compared with stress testing.

Suggesting that the incorporation of High-Frequency QRS analysis into the diagnostic routine may improve the currently deficient diagnostic outcomes in the women population. And may reduce the number of unnecessary angiographic procedures in women.

More clinical studies support the increased sensitivity and specificity of stress HFQRS, or High-Frequency QRS, performed as part of and in conjunction with clinical stress testing procedures.

Do to the limited scope and time of this presentation I did not include here

references to the growing number of studies focusing on the performance of High-Frequency QRS analysis in non stress conditions. And demonstrating its increased clinical accuracy in detecting myocardial ischemia and acute coronary syndrome.

Summarizing the main merits of High-Frequency QRS and the benefits of its inclusion in the clinic work up for the evaluation of ischemic heart disease.

Improved sensitivity decreases the rate of false negative results. Improved specificity prevents or reduces unnecessary further radioactive tests.

Improved accuracy in women allows better clinical evaluation of women for ischemic heart disease and improved standard of cardiac care for these under served populations.

High-Frequency QRS provides the clinician, both in major hospitals and the community with a better tool for an accurate

first line diagnoses of ischemic heart disease.

The technology is very effective in elderly patient populations and currently inconclusive in non diagnostic patients.

Please allow me to conclude. Improvements to first line cardiac diagnostic tests has significant impact on health outcomes, High Frequency QRS analysis during stress testing has demonstrated significantly improved clinical accuracy for the detection and diagnostics of ischemic heart disease.

HFQRS is currently being evaluated in the real life testing under a registry study in several U.S. sites. And this may be an excellent opportunity to provide coverage and capture data at the same time

We believe that devices that incorporate HFQRS analysis in stress ECG testing and that are cleared by FDA should be incorporated in coverage policies of the CMS.

Thank you very much.

DR. GOODMAN: Thank you very much, Dr. Beker. If you could just stay there for just a moment, I want make sure that I understand something.

The device of which you spoke is I believe, listed in the technology assessment, it's listed as HyperQ stress ECG from biological signal processing. That's the same device?

DR. BEKER: That's correct.

DR. GOODMAN: And this was a technology for which the technology assessment team found no in scope studies. It wasn't one of the 11.

DR. BEKER: Not one of the 11, yes.

DR. GOODMAN: Was not one of the 11.

DR. BEKER: It was one study which was not included in the 11 and the study that was just presented here was not yet published or accepted for publication, so they could not

see it.

DR. GOODMAN: Exactly, it went by pretty quickly but I noticed that at least two of the citations that you provided were indeed abstracts not full articles published.

DR. BEKER: One was accepted and other is in preparation as are some other studies, in preparation for publication.

DR. GOODMAN: Okay. Good, I just wanted to make sure I understood that we had identified the appropriate device and understood the publication status.

DR. BEKER: You have, yes.

DR. GOODMAN: Thank you very much, Dr. Beker. We appreciate your time. Thank you, sir.

Okay, panel we're still in pretty good shape on time and I'll just confirm with Maria Ellis one more time. I believe we did not have submitted same day comments, is that correct?

MS. ELLIS: That's correct.

DR. GOODMAN: Okay. So we've picked up a little bit of time there we're actually not too far behind. The portion of our agenda at this point, concerns questions to presenters.

We've already gone down that road a bit so I think we're in good shape. If I could I would like to ask those that have presented this morning to make their way to the front row of the room in case. It's easier for us easier to pick on you. Find you.

And especially the two TA guys pretty close to front and center, and our four presenters, I don't know that Dr. Fleg is still here he's got to leave, there he is. I know he has to leave in a little bit, and Dr. MacLeod as well. So we can now find you, this is great.

Okay, panel, just reminding all of us that while we may have questions a plenty for the material presented thus far today. We

really do want to focus on the questions that we're going to have to answer before we're allowed to leave this exalted hall.

So when you do think of your questions it would help a lot to make sure that you're kind of pinning them to one of our questions. And that we'll try to keep the discussion focused that way. And I saw Dr. Phurrough's hand shoot up right away. Dr. Phurrough.

DR. PHURROUGH: Thank you. Dr. Imhoff.

DR. GOODMAN: We have to all speak directly into our mics I am told.

DR. PHURROUGH: Yes. You listed, on your second slide, three study centers are those studies listed in the reference to the TA as being excluded?

DR. IMHOFF: Correct. That's my understanding.

DR. PHURROUGH: Which are those? Could you just point that out to me so at

some, perhaps at lunch time you can show me what those studies are.

DR. GOODMAN: Do you know off hand the first author of those studies, it would make it easier to find.

DR. IMHOFF: The first author of the German studies is Grube, and the author of the Asian Multicenter Trial is Hosokawa and the author of the Westchester Trial is Weiss.

DR. PHURROUGH: Okay, if I could then skip to one of the two TA people to answer the question of the exclusion of those two particular studies.

DR. GOODMAN: This is Mr. Leisy coming to the microphone.

MR. LEISY: So we have, there are actually four publications from those three cites. Two from the Germany cite from Dr. Grube. And then one is the Asian Multi centers studies to Hosokawa, and the last one is the one from New York which is the Dr. Weiss et al 2002 study.

Now the differences, that was a very good presentation earlier that we saw. They indicated that these studies looked at only the low to intermediate risk patients population.

But the definition for the population was based on the results of the angiographic findings, not on the patient presentation.

And so the criteria that we used was based on the updated American Heart criteria published in 2010 on the management of acute coronary syndrome. Based on the presenting patient, most likely the presenting 12-lead ECG.

And if I can just refresh, it has risk stratification from high risk. Two categories of high risk and then a low to intermediate risk for acute coronary syndrome.

The high risk is the systemic population, ST elevation, myocardial infarction. Another high risk is the STEMI

equivalent or ST depression in the anterior leads and also acute T-wave inversions.

And the last one, the low to intermediate risk for acute coronary syndrome is, patients that present with chest pain and or symptoms suggestive of a coronary event.

That have either normal or non diagnostic changes in the ST or the T-wave. And that was from the 2010 publication of American Heart guidelines for manage of acute coronary syndrome.

So I think the difference in the studies and we really struggled with these studies as well. Because I know they're included in the 2010 report.

Was that the presentation of the patients in these four 3DM studies were all preselected for coronary angiography and their presentation to the clinics or the outpatient centers was not given. And so we concluded that based on all of them being selected for coronary angiography would have selected

patients in a higher risk based on the AHA guidelines of patient presentation. Does that answer your questions?

DR. GOODMAN: Okay. Thank you very much. Further questions at this point. Dr. Steinbrook.

DR. STEINBROOK: This is a question with regard to the technology assessment. And key question 1A when you had the list of the devices, point of information and then a question. The point of information is several of these devices are listed as not FDA cleared.

But I presume that they are still commercially available, that makes no difference in terns of their commercial availability in terms of the way you asked the question. Am I correct with that?

DR. GOODMAN: You need to speak into a microphone, Dr. Coeytaux.

DR. COEYTAUX: Just very briefly with that. We look at those two

independently, whether they were available in the U.S. or whether we found evidence of FDA clearance. We looked at separately. Does that answer your question?

DR. STEINBROOK: No, I'm confused again. It's more just a point of information about the FDA process. For the device to be commercially available in a country does it have to be FDA cleared? That's the question, because are all these commercially available, all of these 11?

DR. COEYTAUX: No. There's one from Slovakia, two of them from Slovakia, the Procardio for example that are not available in the United States and they also happen to not be FDA cleared.

DR. GOODMAN: Commercially available somewhere.

DR. COEYTAUX: Somewhere, but not in the United States. The two can be, you can have one and not the other for that original list, I believe.

DR. STEINBROOK: Probably not worth belaboring but the ones in Table 1, are they all available in this country?

DR. COEYTAUX: No.

DR. STEINBROOK: Oh, eight of the 11 are, the ones that are -

DR. COEYTAUX: Is Procardio in that Table 11?

DR. STEINBROOK: I don't think it is there at all.

DR. COEYTAUX: Okay, that is one they removed it for. Actually I'm going to have Mr. Leisy answer the question because he really focused on Question 1a. Do you want to come up here and address that.

DR. GOODMAN: Mr. Leisy.

MR. LEISY: So on the gray literature search we initially did not exclude devices that were either commercially available or that were not commercially available or were not FDA approved.

We tried to cast a giant, huge net

so we could catch all devices potentially and then any device that we found based on the gray literature research we then cross referenced that based on either the manufacturer website or any distribution website and we attempted to locate a source of distribution.

If we found the source of distribution then we included it as a relevant device. Now we did look for commercial availability in the United States for relevant device where we had difficulty was finding the current FDA approved status for a couple of devices. Are we able to speak on if we found conclusion on some of those?

DR. GOODMAN: The answer to that question was no, by the other staff person from the TA. Dr. Steinbrook.

DR. STEINBROOK: So to follow to my more substantive question, did you in the process of doing your various literature searches for information. Was there any

information available from the FDA as part of the clearance processes?

Or any other FDA activity or submissions to the FDA related to any of these devices which was relevant to your attempt to answer some of the other questions with data?

MR. LEISY: The FDA website was one of the resources we used for the gray literature search. We had a predetermined product codes that were a category of devices that were relevant for our study.

I searched those product codes and we looked at each of the FDA status or applications for FDA status as well for these devices and those that were produced.

I think we found two or three that were, one is the Philips I believe, maybe two Philips devices I'd have to go reference the table. But we did find a couple of devices directly from the FDA website.

We also looked at clinical trials to see if there was any devices pending or

that might have been pending that were applied for FDA status as well. Does that answer your question?

DR. STEINBROOK: Yes, thank you.

DR. GOODMAN: Question, Ms. Cabral-Daniels.

MS. CABRAL-DANIELS: First I want to commend the group for all the hard work that's been done. I do have a question with regard to Dr. Coeytaux, you had mentioned that in looking a the data before and looking at different studies.

I think the question came up with regard to any data with regard to women and you said that was something that you looked at. What other variables did you look at?

Were there any other areas that you might want to share with the panel that you found to be interesting although they may have been somewhat tangentially related?

DR. COEYTAUX: Yes, and I thank you. I noticed that there were good data for

the other studies, the other devices that were included in the TA report on women.

But for the prime ECG my recollection is that they did not have subgroup analyses for women. Part of one of the key questions I believe it was 2b, was to look at factors that effect the outcome or the efficacy and they way the data reported there was just nothing there that we could use, unfortunately.

DR. GOODMAN: And that was Ms. Cabral-Daniels. I mispronounced your name, I apologize. It looks like, Dr. Rudy.

DR. RUDY: Yes, I have a question to Dr. Coeytaux also regarding the data from Ireland, on the prime ECG it's the seems that the bulk of the data came from Ireland.

And then you mentioned something about maybe this data are not really relevant or not really applicable to the way the clinical practice is conducted here in the United States. Can you expand a little bit

about that?

DR. COEYTAUX: Yes, we don't know. Now in terms of the applicability we felt it was our responsibility to at least point out the fact that we had some questions about that.

The two questions that we had about Ireland. One is, two points of comment. One is that they develop the technology and were experimenting with it in the field and they developed in the field and were very good about documenting it in the publications.

Which we would think is a very good thing. But need to be noted because they were developing as their publications, as they were writing their publications. And we wanted to make a note of that.

What we really did not know, nobody on our team could really assess is the impact on the patient population of having essentially a mobile cardiac unit that goes to the field and is staffed by cardiologists,

intensive care cardiologists.

And we just don't know whether or not that reflects a different patient population than those in the United States who tend to be transported to the emergency room setting. So it's a question we haven't we didn't know what else to say.

DR. RUDY: Okay. Thank you, and thank you for all the work you've done.

DR. GOODMAN: Further questions. Dr. Saadi, did I see your hand before or was it Mr. Sampson's hand.

MR. SAMSON: Just a question for the industry speakers. I raised this earlier. I'm curious about the role of the test in relation to other tests.

Are any of you proposing that your technology be used as a replacement for standard ECG or is it generally to be used as an adjunct or an add on?

DR. GOODMAN: This is Dr. Strobeck.

DR. STROBECK: Yes, you know I'm a practicing cardiologist and have incorporated the use of the MCG in my clinical practice over the last two or three years and have found it to be just invaluable. I think this technology because of its accuracy -- particularly because of its equal accuracy between men and women. Can readily help determine who among a group of eight or ten people that you're evaluating with symptoms, suggestive of coronary insufficiency.

No change on the EKG or at least no consistent change -- who have the disease. So yes, I think it can be used and I think that the accuracy compared to SPECT nuclear imaging is significantly better. I think it could ultimately be used as a determinate for who needs an invasive strategy of care.

MR. SAMSON: So you're saying it should replace standard ECG or it should be used as an add on?

DR. STROBECK: Not standard ECG

no, a standard ECG gives you rhythm based information. I mean you get some rhythm based information from the MCG but the MCG's purpose is to detect coronary obstruction.

MR. SAMSON: Okay. So it's an additional test.

DR. STROBECK: It's an additional test to routine EKG.

DR. GOODMAN: Okay. Thank you. This is Dr. Seal.

DR. SEAL: Question on the single study that you presented, I saw differences in percentages but I didn't see any differences in statistical analysis so we didn't see any confidence intervals, or anything like that.

DR. STROBECK: The confidence intervals have been calculated but they don't overlap significantly between MCG and SPECT. Is that what you were saying?

DR. SEAL: Right they weren't presented in your slides, all I seen in the slides was differences in percentages.

DR. STROBECK: Well, the statistical analysis is in the paper. the paper is just recently published I think a copy of it is included in your packet.

But the data was statistical significant at a very high level. When you compared specificity for example between SPECT nuclear and MCG was considerably improved with MCG.

DR. GOODMAN: Based on which study?

DR. SEAL: On the single center study, the paired comparison of MCG with SPECT myocardial profusion imaging. 116 consecutive patients. These are not emergency room patients, these are patients who are referred for consultative evaluation.

DR. GOODMAN: But, Dr. Seal, if I'm not mistaken there was no study that made it through the technology assessment search on this technology.

DR. SEAL: I didn't see it in our

packet.

DR. STROBECK: Honestly I don't understand quite how that happened these are all intermediate risk patients. They perfectly fit the criteria.

Most of them have no resting EKG abnormalities that are suggestive of myocardial ischemia. Nothing to put them in a high risk category. In fact the prevalence of disease when we did the angiography was only 43 percent. So I don't know how these people get classified as high risk.

DR. GOODMAN: Okay. Dr. Seal, just to make sure that we pursue your question, you can have a seat Dr. Strobeck, thank you very much. Do either of our people from our Technoloy Assessment want to comment on why the MCG study did not make it all the way through your process?

You started to address this a bit before, I think when Dr. Imhoff was at the podium, but if you could just clarify that for

us.

DR. COEYTAUX: This is Dr. Coeytaux, is it possible, is there a copy of the paper here that I can read now just to comment intelligently on it?

DR. GOODMAN: That's not a bad question. It's not a bad request, sir. If the folks from Dr. Imhoff or maybe Dr. Strobeck have that study or can find it for us. If not this moment, maybe over lunch. Someone can gin it up for you, I think it's a fair question.

And Dr. Seal, it's an important question to ask and I think we'll be able to return to it.

Dr. Saadi, I think you were in the queue, sir, is that correct?

DR. SAADI: Yes, I think you answered my question, just we actually asked of Dr. Goodman is that of course this technology will provide benefit in one or the other in different populations.

But we have to keep the study population in mind. If I keep that in mind, the Medicare population the U.S. patient populations, so I was actually going to ask you doctor is. As a practicing cardiologist, how do actually see the utility of it? Do you actually have clarified that. That you see this as an add on, right?

And then moving on to the other test procedures. But as a practicing cardiologist are you actually willing to put a patient, okay so I actually see this and it's actually negative. I'm not going to go any farther, are you that confident based on the data actually you have shown?

DR. STROBECK: Well we did analysis, remember these were paired tests. So every patient that was in this trial had both tests. So we re-analyzed the data using the MCG as the determinate for referral for coronary angiography.

And when we did that there were

five patients that had low MCG scores that would not have gone for coronary angiography. But there were 55 patients who had low MCG scores who were ultimately found on coronary angiography not to have coronary disease.

So there's always a little bit. It's not perfect but there is a very, very low incidence of false negatives. And yes, the answer is yes, I would be very comfortable with sending a patient. In other words not referring a patient for catheterization based on a low MCG score.

DR. SAADI: One question.

DR. GOODMAN: Go right ahead, Dr. Saadi.

DR. SAADI: So one last quick follow up question. Would you actually say that based on the data we have. I mean we're talking about a very severe consequence, right? Do you actually feel that we have enough data as of today, based on actually what we have seen this morning to actually

conclude that kind decision. If we miss, I mean I understand --

DR. STROBECK: Basically for evidentiary standards we probably don't have enough data yet. We're in the process of doing a randomized control trial where we compare the MCG score, not just to the anatomic diagnosis of coronary disease.

But to the functional severity based on fractional flow reserve. And we think that actually is going to improve our specificity and sensitivity.

DR. GOODMAN: Good, thank you very much. Thank you, Dr. Strobeck. I'll just remind everyone in the panel that while we are interested in our expert speakers views we necessarily we return to the body of evidence.

And so it's good to hear what Dr. Strobeck might do in practice as an individual practicing physician. That's swell, but we're more interested in the overall body of evidence.

I think that Dr. Beker wanted to make a comment before. Is it still relevant, Dr. Beker? Why don't you approach the microphone, restate the question that you are about to answer.

MR. SAMSON: Is your technology intended to be used as a replacement for standard ECG or as an add on?

DR. BEKER: Right and I just wanted to answer because I think it is a very important question. Some of the technologies, including High-Frequency QRS, this question is not relevant, it's part of the ECG or stress ECG test.

So this is the huge advantage that for some of technologies. For example a High-Frequency QRS is preformed exactly at the same procedure, same electrodes and same placement of electrodes as the conventional stress ECG or resting ECG.

And it just yields double, or additional set of results together with the

conventional clinical and FDA cleared ECG. So it's just like having a super ECG for the same practice or the same procedure of the conventional one.

DR. GOODMAN: Thank you, Dr. Beker. Dr. Fleg, you want to approach the microphone, but I hope you have a specific question that you are about to answer.

DR. FLEG: Yes, I do.

DR. GOODMAN: Please proceed.

DR. FLEG: Well, it's kind of a challenge to the panel actually that when you're talking about the diagnostic value of say the MCG or any of these single averaging tests in terms of detecting coronary disease.

I think that one problem is that none of these tests, at least as I could see from the presentations actually localize where the ischemia is or quantify how much ischemia is there.

When were looking at a patient with coronary disease it's not really

sufficient to say do you have it or do you not have it? We want to know, is this a high risk patient that has a large amount of ischemic myocardia.

Because that's the population that has a much worse prognosis and in whom we would be more aggressive in terms of doing an intervention.

Simply to detect somebody that's got, you know, a single vessel with maybe 50 or 60 percent stenosis is not nearly as important as detecting the high risk patients.

So I think you need to keep this in mind when you are evaluating any of these single averaging technologies. It's probably not sufficient in this day and age.

It's a nice screening test to say, you know, they probably have disease. But we would like to go farther than that. So I don't think that you can, the issue is I don't think these can replace imaging until these test show that they can actually quantify and

locate the ischemia.

DR. GOODMAN: Okay. Thank you, Dr. Fleg. And I'll just remind the panel that while Dr. Fleg's point is well taken, our questions B, all the B's deal with patients of low to intermediate risk, at least a priority.

Okay. Thank you. Further questions at this point for our panelists. Before we proceed to Dr. Rudy, it appears that the TA team may have a response to an earlier question. Is that correct? Sure, would one of you gentlemen approach the mic please?

This concern I believe the MCG technology?

DR. COEYTAUX: Yes, it does. And thank you, Dr. Shen, for this report. This is a study that was just recently published, and was published after the end of our search.

So it appears to be one that would be eligible and we will be, it won't help you today. But we will be doing a revision and an updated search for the final draft. And if at

glance we are correct that it's eligible we will be including this in the report.

The reason that this study here, which is a paired comparison of the MCG, with the system to be a myocardial profusion imaging as a comparator, was not included in the TA report because it was published after the window that we had to work with.

DR. GOODMAN: Okay. Thank you for the direct answer and thank you for on the spot investigative reporting. We appreciate that very much.

And we'll note that typically we are confined to looking at the literature that's A, been published and B, that appears in the Technology Assessment.

But that does not mean that in our considerations that we would necessarily exclude something just because it did not get into a Technology Assessment.

That doesn't mean, however at the same time. That the evidence that may have

been discussed is necessarily rigorous or not. We have to make a judgment about that ourselves, okay? Just to clarify.

Thank you gentlemen for that very timely help. Dr. Rudy?

DR. RUDY: Yes, I have a question, Dr. Shen, and I need some clarification on the technology of MCG. If I understand it correctly MCG's also an analysis approach to the ECG. So you take an ECG and it's just like HyperQ is, except you're looking for something different.

So the question is when I look at your presentation you devise a certain mathematical approach, the LaGrange coordinate, to look at visco-elastic properties of the wall, of the myocardium. And then you use Euler Coordinates to describe the non-Newtonian flow of blood.

But the ECG measures electrical activity on the heart, it doesn't look at motion or profusion. And what's missing in my

mind is how do you go from stress and strain to changes in the electro cardiac activity? And that's even at the single cell level a very complicated story.

DR. SHEN: Correct, it is very complicated. First of all, I think the conceptual approach of this is different because the Einthoven Model is looking at single dipole.

The dipole is emitting three dimensionally, you can measure other, use matching technology or use single 12-lead ECG to detect one lead at a time, and segments of the one cardiac cycle, which is fine, it's a completely acceptable way.

DR. RUDY: I understand, but the measurement is an ECG.

DR. SHEN: Well, we're talking about is that the systems approach, the LaGrange point of view. Actually it was the inspiration for us to look at it.

The entire approach, say what is

the best way to extract more information out of these ECG signals? Rather than looking at the traditional way we stepped back and looked at the LaGrange approach.

The instruction to us immediately was that you need to look at the information between the two signal sources. That's the one screaming headline to us. Was that you cannot look at a single lead at a time. You have look at both leads.

Then what happens is the information actually traversing, communication between these two parts as systems approach The principle thing, the first thing is to dissect the system into different parts and see how they communicate with each other.

So we're looking at actually for instance cross power spectrum. Cross power spectrum actually is looking at the power distribution at a frequency of a lead two frequency with V5 power distribution.

Now furthermore, look at the

histogram, it is the impulse response. Impulse response is actually looking at the relationship between how the V5 signal is received or reflected by the Lead 2 signal source.

And so you can actually by using this mathematical relationship, you can actually understand how the compliance of the response of different signal sources give you extra information.

That is why we decided to proceed with multiple mathematical functions. Each one of them will give you the information that is unique rather than the -- I'll be happy to go over the math with you, one by one, all functions.

DR. RUDY: I didn't want it to go so long. Just to clarify.

DR. GOODMAN: Gentlemen, we have to speak one at a time please. Dr. Rudy, proceed.

DR. RUDY: Just to clarify, all

the signals that you are measuring are ECG's?

DR. SHEN: Correct.

DR. RUDY: Okay, thank you.

DR. GOODMAN: I'll also just remind the panel, the electro physiology and the math is fascinating but do remember that are questions start with detection and move on to physician behavior, patient outcomes and so forth. So the math is great but we don't have a math question.

Further questions at this point for our panel. Is that Dr. Heseltine?

DR. HESELTINE: Yes, one question for Dr. Shen. You mentioned in your presentation that your system detected not only ischemia but other pathology. If we exclude arrhythmia detections, arrhythmia pathology what are we left with if it's not ischemia?

DR. SHEN: Hypertrophy can be non ischemic or ischemic, but it changes the heart shape. Actually this technology can be used

to measure remodeling, gradual remodeling as a result of a valve disease. For instance someone has a atrophy of the aorta valve stenosis over time the left ventricle, will eventually evolve. And actually the system can be used to measure that, that measuring without even having to do with anything with ischemia.

DR. HESELTINE: And that's different from the 12-lead EKG which also detects hypertrophy?

DR. SHEN: That's different, the way that's measured, we're measuring entire different things.

DR. HESELTINE: Thank you.

DR. GOODMAN: Good, thank you. I have a question. Starting with out TA people. Back to kind of a higher order question. We have pair of questions, actually for us they are Questions 3 and 4. That deal with the impact of this type of technology, and physician decision making.

And if I read the TA correctly you found zero studies addressing physician decision making. I just want to confirm that that is correct.

Okay, do any of our speakers have published peer reviewed evidence, not to be published or just in an abstract that any of these technologies are shown to effect physician decision making?

Okay, apparently not, okay, good. I just wanted to make sure I understood that. I apologize if I'm the only one who wasn't sure about that.

And then we have a pair of questions in with patient outcomes, for which the TA discerned three studies. And if you don't mind, can I ask our TA people to come up and just briefly recap what those three studies were?

And for what technology they apply? There were three of them. And chances are at least two of them had to be the prime.

DR. COEYTAUX: This is Dr. Coeytaux, my recollection that there are two studies. Please correct me if I'm wrong, you have the report, is it three? There may have been three papers, to OCCULT trials and then one by, the last name, the first author is escaping me. Two studies?

DR. GOODMAN: Yes, you're right, there were three papers.

DR. COEYTAUX: So very briefly by memory here, the OCCULT trial is the only study that published the findings of the data they collected. And it had to do with looking at the outcomes of patients who had STEMI as identified by the prime EKG compared to the ECG identified STEMI patients.

That's the only piece of data that I think we found, would you like me to repeat that?

DR. GOODMAN: So it was prime versus the ECG?

DR. COEYTAUX: Prime versus the

ECG in terms of identifying STEMI, ST elevations. Identifying ST elevations.

DR. GOODMAN: But is that improving patient outcomes?

DR. COEYTAUX: So the reason, I mentioned before about the mention of limited evidence. The reason we chose to bring this to the level of discussion and bringing it up is because there may be.

There's two ways of interpreting this data as I can see it. There are two, it may be important data, but I don't know. The reason we brought this up was because it was there in the section of the paper that talked about prognosis, events that happen after the initial diagnosis.

The way I can interpret this data, the only two ways I think I can think of is that it's interesting that there's a prime EKG that identified ST elevation. And they found that of those people, of those patients there was significant mortality. There was a bad

event associated with it. That's what I would call it.

Whereas the ECG, that identified an ST elevation there was no such worsening of outcomes to those people. So there was a difference, they identified two different outcomes based on a test at a given period of time.

DR. GOODMAN: That is prognostic information. Not information about the impact of diagnostic technology on patient outcomes.

DR. COEYTAUX: That's a fair statement, I think both are fair statement, it is prognostic but it may be because of outcomes it may be because. It could be, and this is where I was getting to about the two ways of interpreting it.

It could be that the prime ECG identified a different, slightly different population. They did identify a slightly different patient population. Some people had ST elevation on one test and not on the other.

So it could be that the difference in population had different prognosis, therefore it would be a prognostic issue.

I could also be that a decision could have been made, based on the findings of the prime ECG, that lead to a change in outcome. We don't know.

DR. GOODMAN: But no study that you reviewed actually was designed to detect a causal relationship between the test and the patient outcome?

DR. COEYTAUX: That is absolutely true, there's no question about that. This is a secondary finding that we chose to elevate to the point of this discussion. But it's fraught with the potential concerns that you are mentioning.

`That it was not designed to do this, it was a secondary finding that we reported because we found it and we stated because it may have implications. But it is far too early to conclude one way or the

other.

DR. GOODMAN: So, let me make sure I understand this. No study was designed to detect a causal relationship?

DR. COEYTAUX: Absolutely true.

DR. GOODMAN: A couple of articles reported finding that what happened later to these folks was different?

DR. COEYTAUX: Yes.

DR. GOODMAN: But there's absolutely no evidence that that had anything to do with their having had a test or not?

DR. COEYTAUX: There is no valid evidence, there is just, yes, I certainly agree. It is in a report that there were outcomes that differed.

And the study was not defined, designed to look at this, there's no causality that can be definitively inferred. But the data were there and we're presenting it for discussion.

But it a very weak level of

evidence. And it is one that has inherent bias for the reasons that you're mentioning.

DR. GOODMAN: I think you made a generous inference there but we appreciate your inclusivity. Thank you.

DR. COEYTAUX: You're welcome.

DR. GOODMAN: I believe that's Dr. Imhoff, sir. On this issue? Thank you. Dr. Imhoff, you're about two meters tall so I don't know if you want to bend down or lift the mic, but we want to make sure, either way we want to make sure we hear you.

DR. IMHOFF: I'm just speaking out loud so I think that you can hear me. I just want to make a very general comment about the diagnostic test, or the general diagnostic test that we are looking at.

Diagnostic tests as such cannot have any impact on outcome with the exception of direct complications from a diagnostic test for coronary angiography. It can only have impact on outcome if a therapeutic decision is

influenced by this test.

And then this decision is also enacted in therapy and therefore none of the studies that I'm aware of would fit into the category.

DR. GOODMAN: Thank you, sort of Dr. Imhoff. I appreciate your view point, I don't agree with your finding. There are many cases where screening tests or diagnostic tests a study of those has been designed to follow a set of patients, whether it's in an RCT or some other study where a causal finding can be made.

That's why we do these tests is because we want to improve patient outcomes. Ultimately we appreciate that the relationship may be indirect from time to time.

But we're looking at the questions asked here and I think it's been confirmed that nothing was found about influencing a decision.

And it sounds like nothing was

found about improving a patient outcome from a causal standpoint. However hard that may have been to establish, it doesn't appear that anything was found.

Did the gentleman from the TA have anything to say on that? You started to approach the mic but I think now you've took your seats again. If it's really important we'd be glad to hear it.

MR. LEISY: Philip Leisy again. It's on this same issue that we've been talking about. It goes back to the OCCULT trial, when we looked at patient outcomes and they're finding was that the 80 lead only ST elevation patients versus the 12-lead only ST elevation patients.

The door-to-sheath time, or the time between presentation of symptoms and intervention, was much greater for the 80 lead only ECG.

The time difference if I could find in here, was for the 12-lead only, for

the 80 lead only was greater than 1,000 minutes, door to intervention.

And with the ECG 12-lead only was less than 60 minutes, 54 minutes. So that could potentially be, while they did not attribute the poor outcomes to that finding that was a finding in the result of that report.

DR. GOODMAN: Okay. So it's possible that in that study, which may or may not have been designed, to detect that difference that you just cited. That perhaps action was taken more rapidly in one instance than another?

MR. LEISY: Correct.

DR. GOODMAN: Perhaps, and that doesn't mean that one can confer that having taken that action any faster or slower might have effected the patient outcome?

MR. LEISY: Right.

DR. GOODMAN: It's possible, possible it might have reflected a change in

clinician decision making. Again just possible, the studies weren't designed to detect that I don't think.

MR. LEISY: Correct.

DR. GOODMAN: Okay, thank you for noting that. That's very helpful for us.

MR. LEISY: You're welcome.

DR. GOODMAN: We'll take one more question before the lunch break, Dr. Janowitz.

DR. JANOWITZ: I just want to ask anyone on the panel if anyone has data concerning use of this technology in asymptomatic patients?

DR. GOODMAN: No one is approaching the microphone Dr. Janowitz. Thank you. Dr. Phurrough?

DR. PHURROUGH: I was going to ask this question too. In your slide ten Dr Imhoff, you specify MCG was validated in patients with indication for coronary angiography including asymptomatic patients. So that seemed to be a positive to Dr.

Janowitz question?

DR. IMHOFF: Yes, but I refrain from answering that question because we did not explicitly analyze that sub-pool. Therefore we have no data to present on asymptomatic patients only. And I think that was the question.

We had a mix of patients that were symptomatic A. Symptomatic were scheduled for coronary angiography so chronic CAD with or without symptoms. So I cannot say anything statistically relevant about this subgroup asymptomatic patients.

DR. GOODMAN: Okay, thank you. Dr. Coeytaux, if you could approach the mic just one more time. I just want to make sure I understand this. On the asymptomatic. I'm sorry to be redundant about this.

You stated earlier that your search strategy was not designed to exclude asymptomatic patients? So in your judgement you would have captured studies on

asymptomatic patients had they been in there?

And however it's possible that the people that were doing hand searches might have set a study of that type aside. I think you said it was unlikely but it's a possible, is that correct?

DR. COEYTAUX: That is correct. If I might take one minute to expand upon it, because it is such an important question. That is correct, everything you said, I agree with entirely.

But I do want to say that we approached this task with a clinical scenario in mind of this technology being used to assess patients in real time who might have ischemic heart disease. Therefore that is the mind set, that is what we did.

The study on the search strategy absolutely included the whole universe of patients who could fall into any of these risk groups. In the second stage, so I'm very confident that we did not exclude anything

structurally by the search values. I'm confident about that.

But going forward from there in deciding and applying the criteria and looking at the titles and then further at the full text review.

I certainly and I believe all my colleagues are who also were doing this were thinking in the clinical scenario of patients who have some reason to be evaluated for ischemic heart disease. That's how we went through this.

Now we had further discussions afterwards about making sure that question of asymptomatic on patients was addressed in preparation for this meeting.

So what we did then is we went back to our search strategy, we looked a the group I think of 58 studies that had been excluded for patient population. Looked very carefully at those to see if we excluded for asymptomatic reason, and we did not.

DR. GOODMAN: You took a step to actually go back and see if yo had done that?

DR. COEYTAUX: We did take that step. We did officially take that step which is a little bit out of protocol because we had already gone through that process.

But since we had already, since we routinely and by protocol separate out the reasons why, identify why we excluded studies. We had a category of not population of interest.

So I personally went back to all 58 of those and looked at those to see if maybe we had, for whatever reason, excluded for reasons of asymptomatic. And there were none.

And that gives me great confidence to say I really don't think that in the entire body of studies that we first collected in the 2,000 or so that I'm very confident that none of those have asymptomatic patients.

DR. GOODMAN: Okay. Thank you

very much. Panel this happens from time to time, given the time difference between when for when CMS asks for an assessment to be done and when we actually have our meeting can six months, eight months. Sometimes a year or more.

So we do need to acknowledge a bit of a disconnect between the questions that were asked of the TA folks and the questions that we're asked to answer.

So we've been trying to extract whatever we could at this point about that issue on our Question 1a and 2a and so forth about asymptomatic patients. So I think we have an imperfect answer to this but a partially useful one.

With that let's take our lunch break. I hope you don't mind, we've stolen six and a half minutes from your lunch. Let's, never the less, meet here at 1:00 p.m.

Thank you, this has been a very helpful morning to all of our speakers,

panelists we very much appreciate your information and attention. See you at one.

(Whereupon, the above-entitled matter went off the record at 12:08 p.m. and resumed at 1:02 p.m.)

DR. GOODMAN: We will get started, I'll ask again if the folks who've been our presenters and our TA folks could come to the front of the room it would be helpful.

As noted before we do have this main job of our panel does, of answering these ten questions. The four times two plus the two questions.

And I think we will probably proceed to get into the questions pretty soon. But before that I think we've got some clarifications we may want to make here.

And if I can pick on Dr. Phurrough, if he doesn't mind, one of the issues, Dr. Phurrough that came up was perhaps a need for clarifying matters of asymptomatic and some other definitions.

Have you, starting really with the first question. Did you want to clarify that for us, or pose that for us?

DR. PHURROUGH: Well, I think I understand asymptomatic versus with and without chest pain. I think there's been some lack of clarity between what we've heard from the TA and what we've heard from the various presenters and what the questions actually are.

So I think it would be helpful for Dr. Rollins or Dr. Miller or someone to try and clarify for us the differences in A and B just to make sure that we're clear and then that may lead to a couple more questions to the presenters.

DR. GOODMAN: Okay, and when you say A and B you mean for example in Question 1a being, reliably and accurately detect coronary artery disease in asymptomatic patients at risk for the disease.

And B, patients with signs and

symptoms suggestive of ACS with or without chest pain. That distinction? Okay.

And I'm going to give a little heads up to Dr. Steinbrook, who I think was, needed a bit of clarification about whether we've got a comparator here or not. So Dr. Steinbrook, you're on notice for raising that issue.

Let's get started here, McDonough coming pretty soon. Dr. Rollins and or Dr. Miller?

DR. ROLLINS: I'll go ahead and get start. In terms of A, coronary artery disease in asymptomatic patients at risk for disease. That would be an individual who does have CAD but they're void of any symptoms.

They have no chest pain, they may not even have any symptoms, other signs of CAD such as shortness of breathe or dyspnea or other types of characteristics.

Whereas B, patients with sign and symptoms suggestive of ACS with or without

chest pain. That would be a patient with acute coronary syndrome, some with chest pain and some without chest pain.

Those without chest pain would still have the other symptoms related to CAD such as shortness of breath and those other types of activities associated with those conditions.

DR. GOODMAN: And let me also note, because you do put in the preamble of our questions that B specifically talks about low and intermediate risk. Patients at low or intermediate risk. Yes, Dr. Miller?

DR. MILLER: We have for B, we are looking at patients with signs and symptoms suggestive of ACS who are not triaged for emergent reperfusion therapy.

As we were thinking of those patients we were using the American Heart Association, 2010, I think it is guidelines That have been previously mentioned. In which the American Heart Association divides

patients into three categories should they come into your medical facility for symptoms of ACS.

So STEMI patients or STEMI equivalent patients are those that are assigned a very high risk by the American Heart Association. And it is advised that within a very short period of time they are prepared and initiated to have a some sort of reperfusion therapy.

So those patients would not necessarily have further testing done upon them than the usual 12-lead ECG and then there would be a decision point and they would go off to their therapy.

For those patients who have unstable angina, non-STEMI's non-diagnostic ECG and what am I forgetting here. And a normal ECG but who have a reasonable history of ACS like symptoms. It would be very likely that they would have other testing done.

So that is the population that we

are talking about today when we say that they have low to intermediate risk and the corollary of that for us was that they would not be immediate candidates, or I'm sorry, urgent candidates for reperfusion therapy.

DR. GOODMAN: Dr. Phurrough?

DR. PHURROUGH: Just a bit more clarity on asymptomatic. Let me just ask, are we talking about patients who have never had any symptoms, related to coronary artery disease?

DR. MILLER: Yes.

DR. PHURROUGH: Or patients who are currently asymptomatic but may have had a diagnosis previously?

DR. MILLER: No, we are talking about absolutely no symptoms but you have a high, they have high risk and you, their physician, has high suspicion of the fact that they may have coronary artery disease.

DR. PHURROUGH: But not based on symptoms?

DR. MILLER: Not based on symptoms.

DR. PHURROUGH: So with that definition, are any of the patients that have been included in the studies that we're talking about today fit that category?

DR. GOODMAN: This is Dr. Strobeck.

DR. STROBECK: Yes, I've had patients come to me for evaluation of an abnormal EKG for example. The development of a right bundle branch block who participated in my trial because there was a concern on the part of a referring physician that this patient may have underlying coronary disease but they've had no symptoms whatsoever.

The abnormal EKG is difficult sometimes to evaluate using traditional stress testing methods and we found that the MCG was very helpful because it would. The accuracy is independent of the EKG morphology. So those patients were in there.

DR. PHURROUGH: So there were patients who had an abnormal ECG and agreed to enroll. Never had symptoms, agreed to enroll in your trial, and had either ECG or SPECT and then went on to CAD?

DR. STROBECK: Went on CAD if the SPECT was abnormal.

DR. PHURROUGH: If the SPECT was abnormal. Okay.

DR. GOODMAN: So Dr. Phurrough, are you satisfied that you got a good answer to your question?

DR. PHURROUGH: I have the answer, yes.

DR. GOODMAN: Hold on, Dr. Seal. Dr. McDonough is your question pursuant to this point or a different one? Okay. Then we'll return to you. Dr. Seal, is yours about this point?

DR. SEAL: Yes, it's about the same population, so is this was the single center, 116 patients?

DR. STROBECK: Correct.

DR. SEAL: How many patients were asymptomatic of 116?

DR. STROBECK: There was just a handful, probably ten to 15 patients.

DR. GOODMAN: Okay. Thank you, on this point, it was initiated by Dr. Janowitz.

DR. JANOWITZ: It seems to me we're excluding a large group of patients who are not acute coronary syndromes but who present to their doctor with either atypical chest pain or some symptoms suggestive of heart disease.

And those seem to be the majority that goes for the noninvasive testing and stress testing. How do those not fit under that A's please clarify?

DR. GOODMAN: The A's are coronary artery disease to detect CAD in asymptomatic patients at risk for disease.

DR. JANOWITZ: Right, but most -- many of them are symptomatic. And they don't

fall under B either.

DR. GOODMAN: Well, B I would take as patients who are presenting to the emergency room with suspected acute coronary syndrome.

DR. MILLER: I'm sorry, I should have clarified. The B patient we are considering is if they did have symptoms, someone comes in to you says last night I was short of breath for 30 minutes and I rested it went away, I'm fine. Okay. That patient we would put under B. Okay? I'm sorry I wasn't clear.

DR. GOODMAN: Thank you, Dr. Miller, just to remind folks. This is Dr. Heseltine.

DR. HESELTINE: So, Dr. Miller, when you started to describe Group A, I thought I understood quite clearly that these were asymptomatic patients. And that they didn't have findings other than broad findings.

But then I watched your face as we discussed the issue of abnormal electrocardiogram but non-diagnostic. Where are you placing those patients?

DR. MILLER: For example, the example that Dr. Strobeck gave. We had not considered that, personally I would put them in B. I would consider the abnormal ECG as being a potential sign or symptom of significant coronary artery disease.

DR. HESELTINE: Yes, but you say ACS is the definition.

DR. MILLER: Right, you're absolutely right.

DR. HESELTINE: And that's a syndrome and either you have it or you don't. Most people might make the argument that somebody comes in even with a left bundle branch block isn't necessarily somebody with ACS.

DR. MILLER: Yes, so I think, to be perfectly honest we hadn't considered that

group of people.

DR. GOODMAN: Okay. In the preamble to the questions though for the B's which correspond to the preamble Number 2, in patients who present with signs or symptoms of ACS, with or without chest pain.

It also says of low or intermediate risk for ACS which is thereby defined, thereafter defined as signs or symptoms of MI and 12-lead ECG demonstrating unstable angina non ST elevation, MI or nondiagnostic.

So there are going to be, for the definition of low or intermediate risk for ACS signs or symptoms of MI and those other things.

So I think that helps draw the line a little bit more clearly. Dr. McDonough, next on this?

DR. MCDONOUGH: Sure, on a different issue about the same question.

DR. GOODMAN: Okay, we cool with -

- are we okay with this part of the question so far? Steve, back to you, he's nodding his head. Dr. Heseltine, close enough at this point?

DR. HESELTINE: I don't, to your point I think a substantial number of patients are being excluded by both questions. If you don't have ACS, and you have abnormalities, it seems to me that they could be included in A.

And if that's where you want to put them that's fine. But what I'm hearing is a variety of people putting them B or A.

DR. GOODMAN: Okay. When it comes time to answering our questions if there is some grey area there aside from any vote you may offer? We'll take your comments to accompany those because we want the agency to have those clarifying discussion points as they go forward. Thank you.

Dr. McDonough, thank you for your patience.

DR. MCDONOUGH: I'm looking at

Question 1b, and it appears there is, maybe it's obvious but I want to make it absolutely clear. There is a word or a phrase that's missing.

"Are able to reliably and accurately detect, what, in patients with signs and symptoms of acute coronary syndrome."

Is it coronary artery disease which is an anatomic diagnoses or is it myocardial ischemia or is it necrosis, myocardial necrosis? What are we talking about?

DR. GOODMAN: Let me offer this. I think the answer to that is you are correct. The question is not worded accurately, but the preamble which explains why these questions are being ask does.

The preamble which starts the second paragraph, the questions below refer to the use of, et cetera. It says for the purpose of detecting CAD in 1, patients who

are asymptomatic, 2, in patients who present.

So what 1b should say is, coronary artery disease in patients with signs and symptoms.

DR. MCDONOUGH: Coronary artery disease?

DR. GOODMAN: Yes, because the transposition from Paragraph 2 in the preamble, to the wording of the Question 1b did not pick up the phrase CAD. In both instances, when it should have. At least that's my understanding of the intent of the questions.

And I don't see Dr. Miller disagreeing. Thank you for picking that up, a good grammar teacher would have detected that as well. Dr. Janowitz.

DR. JANOWITZ: I hate to be nit picky about this but I would request that we say obstructive coronary artery disease. Because many people have non obstructive coronary disease.

DR. GOODMAN: Okay. That is a very good point to make and I will defer to some of our cardiologist friends. Because we did see different forms of CAD in our presentations today.

I think we saw spasms, and we saw things other than the blockage, correct? Dr. Rollins and or Dr. Miller, what is your, what's your intent on this? CAD, is CAD confined to, what blockages to use the colloquial term, or the other forms of CAD? You can think about that for a moment, or confer.

DR. HESELTINE: Can I add to that question?

DR. GOODMAN: Go right ahead, Dr. Heseltine.

DR. HESELTINE: It seems to me that dancing around the word usage here, which comes from different disciplines. Actually obstructs the purpose of this. Which is why are we investigating these patients at all?

And essentially I would think that it's to either, diminish, prevent, or alleviate ischemia. Which eventually might go on to damage the heart, and obviously does.

So it seems to me that that's where everything, if you'll pardon the pun, flows from. So I would include the real meaning here of the intent. I interpreted the intent to mean what we're driving at is can we use these systems to detect patients who are either ischemic or likely to be ischemic or could become ischemic soon.

DR. GOODMAN: So the broader definition of CAD. As opposed to the more narrowly defined. Dr. Miller is nodding her head, and Dr. Rollin's is also nodding his head. It seems as though the agency would concur.

Thank you, Dr. Janowitz for bringing up that point. This is all necessary, we have to nail this all down. Dr. Steinbrook, sir.

DR. STEINBROOK: Thank you, I have a slightly different question, but about the same set of questions, 1 and 2. So it says these technologies were able to reliably and accurately detect CAD. So what is the standard of comparison here?

In other words, if we're thinking about these in the context of the standard EKG I might think about this differently than if the standard of comparison is coronary angiography.

It would be helpful to have, and some of the studies which were reviewed in TA were looking against standard EKG's. So it would be helpful to have some clarity as to what you're trying to get at with this question.

DR. GOODMAN: And Dr. Miller, if you and or Dr. Rollins might approach that. Just in one word we're wondering if you've got a comparator in mind. And if so, is that ECG or is just against nothing, versus nothing.

DR. MILLER: I think the key to that question is in Number 5, or to your question, Dr. Steinbrook.

In question Number 5 we are asking whether or not there is any incremental information obtained from these new technologies, beyond that that is provided by the ECG. This is the 12-lead standard ECG.

DR. STEINBROOK: So in thinking about how we would respond to Questions 1 and 2 we should basically read them as if Question 5 even thought that's not actually the wording here?

DR. MILLER: Well, one and two have to do with, do you believe that the SAECG technology, as a stand alone, is able to reliably and with validity, and accurately detect coronary artery disease, myocardial ischemia in these two sets of circumstances, compared. Do you believe that it is possible to do that clinically at this stage in time?

DR. STEINBROOK: That's really,

then comparative just for Questions 1 and 2 is nothing.

DR. MILLER: Right.

DR. STEINBROOK: Not anything else?

DR. STEINBROOK: Okay. That's very helpful because it was for the reasons I stated it was unclear to me how we should be doing the question.

DR. GOODMAN: Okay. Good, so the comparator is nothing in particular at this time. Although we would anticipate by the time we get to Question 5 that the marginal difference would be of interest. But for one and two it is not. Thank you, excellent. Dr. McDonough.

DR. MCDONOUGH: Just also for clarification, I hate to pick on things.

DR. GOODMAN: Go right ahead, Dr. McDonough.

DR. MCDONOUGH: Are we going to vote on different technologies? I mean, my

answer on say vector cardiography, may be different than body surface potential mapping. Or are we thinking of these just in general? These technologies, one vote.

DR. GOODMAN: Given the scope of the evidence. Well first of all, given the scope of the evidence it appears that we've got peer review literature on just a couple of them. Two of these, ten studies on one and one study on the other.

So our n is pretty small, I would say that our deliberations will be reflected in two ways. One the vote, two the discussion points.

And I would recommend that if the questions about adequacy of evidence, what the evidence demonstrates. As long as there's adequacy of evidence for at least one, you can vote that way. And proceed thereafter. But our discussion will make clear to which we were referring. Okay?

But I'm glad you ask the question,

it's not kind of average or kind of the net overall, if at least one of these things is hitting buttons someplace we'll want to know about, you can vote that way.

Unless, I don't see any disagreement on that. Hello, Dr. Miller.

DR. MILLER: Correct me if I'm wrong but the TA limited itself to body surface mapping, and those signal analysis technologies that used a mathematical conversion. And if you give me a second we can look that up in the TA.

DR. GOODMAN: Well, allow me to interject, the preamble, defines SAECG technologies as one, assess electrical activity to the heart. Two, transform or interpret the signal through spacial imaging or advanced mathematical modeling.

DR. MILLER: Right, so the -- did you include any, and I'm addressing this to the writers of the TA. Did you include any other technologies outside of the body surface

mapping in terms of the spacial imaging?

MR. LEISY: Philip Leisy here to answer. Yes, we did include each of the technologies and devices that were shown in that table above in the presentation that had about 12 or so different devices.

So we did include the signal average ECG which is that the LP3000, the body surface mapping. We included the mathematical analysis, which is the 3DMP, we also included vector cardiography. There are two devices that had vector cardiography.

And there were also the HYPERQ ECG's as well were included. The only reason that none of those other technologies reproduced studies because none of the studies fit the inclusion criteria.

DR. GOODMAN: Thank you. Can I call Dr. Louis Jacques to the microphone please?

DR. JACQUES: Hi, I'm Louis Jacques, J-A-C-Q-U-E-S. Just to reenforce

what you said, many times, for MEDCAC's what is more informative than any particular voting numerical result are the actual conversations around that. We do not currently have an open national coverage determination on any one of these proprietary technologies now.

And based on what I've heard during this morning and parts of this afternoon in fact, the greatest value of some of your deliberations or comments may be to specifically highlight areas where you may like to see more.

So in that result -- nobody's going to die based on your vote. Okay? So if you believe that based on any of these technologies that you feel confident enough to name a particular score, feel free to do so.

Because we will find from your comments about your vote whether you were really aiming at one or the other or a more general statement.

DR. GOODMAN: Thank you for that

clarification, Dr. Jacques. All right. Any other questions, and just a little bit of warning here. I sense that pretty soon we are actually going to start answering these questions. Not just at this moment.

Just kind of a preamble or just kind of explanation of how it's going to go. Is that as we approach each question, we're not going to dive into the Likert scale grading right away.

I will probably want to ask the TA team to provide a synopsis, a real distilled synopsis on what they found relative to the question that's going to be on the table at the time. So we're going to want your kind of, you know, highlights here.

And then we might also call upon any of our other speakers who are highly confident that they have an important point to make on that particular question that we as voting -- that our voting members need to know.

So just a little warning that once we get into voting, it doesn't mean you are off the hook. Especially you TA people, I'm going to ask you to think ahead about a synopsis reach. Got it? Good, thank you. Dr. McDonough?

DR. MCDONOUGH: Dr. Strobeck presented a study which was not included in the TA but would have met inclusion criteria. I haven't reviewed it other than what we've been presented. Do we consider it?

DR. GOODMAN: This was the study that the TA folks thought would have met there inclusion criteria but was published this year. So recently that it predated the time of your work.

Again since we're not voting on the issue. Dr. Rollins, did you want to comment?

DR. ROLLINS: Even though this article has been published, I guess since our information went out, did everybody have

access to it? And was able to read it?

DR. GOODMAN: No. That's what I'm coming to. So what we need to do is acknowledge that the study exists, we've heard a little bit about it. But we don't have it in front of us. So I don't think that that's going to weigh very heavily.

We cannot tell you to not consider that, as an individual from public or private sector who's making some judgement here. But if it's not in front of you and not in the evidence table you probably have less to go on there.

DR. ROLLINS: And also you don't have the capacity without seeing it, to actually assess it and take a look at it and make sure that the, you know, from an evidentiary perspective that the methodology was correct in, you know, those type things.

DR. GOODMAN: Right, so that's just an adherent kind of problem we have sometimes. It's a matter of lag time. But I

was the chair can't tell you to not think about it if you so choose. Dr. Cabral-Daniels.

MS. CABRAL-DANIELS: Just a point fo clarification, did I understand that the technology assessment folks said that it may likely have met the criteria. But was a definitive decision made on that?

DR. GOODMAN: Yes, as everyone recalls the TA folks did a quick look at the article. The hard copy that was handed to them late this morning.

DR. COEYTAUX: Yes, and I neglected to say the publication date, which was October, so just very, very recently came out.

DR. GOODMAN: October 2011?

DR. COEYTAUX: 2011, yes, October 2011.

DR. GOODMAN: That would be recent.

DR. COEYTAUX: Yes, and our search

actually went into October, the Medline search so it was right outside -- we thought we had a very recent one but there is still some time that elapsed.

Both of us looked at it quickly and it looks as though it would be included. But I do want to highlight that I wouldn't even be able to make that determination now even spending more time because we have to go through an independent process of two individual independent decisions to be made.

So I think it's likely, as you said, yes, to the likely, but I can't attest to the certainty of that.

DR. GOODMAN: Thank you. And I'll just remind everyone of Dr. Rollins comments a moment ago about, it's not in evidence until you can rigorously assess its quality and so forth.

Okay, other kind of general questions before we kind of move, before we do move to the questions themselves? Is there

anything that should be on the table that's off. Are we missing an important piece or type of evidence? Any kind of clarification on important matters of definition here? Dr. Saadi, and please speak directly into the microphone.

DR. SAADI: Sorry, just the same question again. Dr. Miller, actually it's for you. The Questions Number A right? When is asymptomatic patients that at risk for the disease so they just would be in our elevated LDL and all these other things and you know, the averages of smoking. Do want us to consider those? Is that what is the definition of the risk?

DR. MCDONOUGH: Yes, someone who would be at high risk for coronary artery disease as you would define it as practicing clinician. So for example, someone who has diabetes, yes.

DR. SAADI: Okay. Thank you.

DR. GOODMAN: All right then,

we're going to proceed now to Question 1. And recall that this is one of our adequacy questions, it's not a question of whether something works or not, it has to do with what you think of the adequacy of the evidence on that issue. And we'll take them, 1a, followed by 1b.

And do recall now given somewhat of a clarification. Question 1 is "How confident are you that there is adequate evidence to determine whether or not SAECG technologies" Could be any of them remember? "Are able to reliably and accurately detect 1a, coronary artery disease in asymptomatic patients at risk for the disease." And remember that this adequacy is not with regard to a particular comparator? That was a clarification.

Now before we do the voting, I'm going to ask our TA folks if they could, if possible, I know this is kind of tough to do on the run here. If you could summerize, as

well as you can, what you found regarding 1A? Asymptomatic patients and so forth.

MR. LEISY: Certainly, so in our task, we were tasked to identify these two very different patient populations. The one the coronary artery disease which is an anatomical problem as Dr. McDonough addressed earlier. And the ACS which is the a physiological representation of the anatomical problem.

Now with 1a, coronary artery disease and asymptomatic patients, we did not find very many studies. None of the included studies included coronary artery disease specifically. They all addressed acute coronary syndrome.

DR. GOODMAN: None addressed --

MR. LEISY: Specifically none of them addressed coronary artery disease at presentation. Each patient had a suspicion of acute coronary syndrome.

DR. GOODMAN: Okay. But it was

none?

MR. LEISY: Correct.

DR. GOODMAN: Okay. Any comments from our speakers, laser-pointed on that issue, 1a? It looks like Dr. Strobeck is approaching the microphone.

DR. STROBECK: Yes, again, I tend to agree with Dr. Janowitz, it's very difficult to find a population of people that are at high risk that are absolutely 100 percent asymptomatic.

Somebody will have an atypical discomfort or have an abnormal EKG. So the study that I spoke of specifically included patients who would have otherwise been considered asymptomatic.

DR. GOODMAN: And that was the most recently published.

DR. STROBECK: The most recent trial comparing MCG to SPECT.

DR. GOODMAN: And that was just about it, huh? That's about all it got to go

on even from your?

DR. STROBECK: Yes, I have not done a study specifically dealing with absolutely asymptomatic people. I thought that was a screening test and I didn't think that the purpose of this would be for screening.

DR. GOODMAN: It's asymptomatic but having increased risk factors for CAD. Thank you doctor. Any comments on our panelists about 1a? Adequacy of evidence. CAD, asymptomatic patients versus no comparator in particular. Dr. Steinbrook?

DR. STEINBROOK: To clarify, are we voting on 1a and 1b separately?

DR. GOODMAN: Yes, we're going to vote on 1a and 1b separately. Okay. Ms. Ellis, did you want to remind us about how we push buttons or anything like that?

MS. ELLIS: Basically all you have to do is push any number one through five. For your voting scores, you can press it as

many times as you want but the last push will be the recorded score.

DR. GOODMAN: Okay. So Likert scale, one is low confidence, five is high confidence, three is intermediate confidence.

How confident are you that there is adequate evidence to determine whether or not SAECG technologies are able to reliably and accurately detect coronary artery disease in asymptomatic patients at risk for the disease.

One is low confidence, five's high confidence. And what will happen is once we have a vote from everyone then the results magically appear on the screen. This machine sure makes a lot of noise.

MS. ELLIS: I was told that CMS is working on getting a quieter projector soon.

DR. GOODMAN: But we can't wait that long today, right.

MS. ELLIS: At this time we have six votes, so if every one can make sure that

they actually pushed the keypad, okay. We have all the votes with mean score of 1.375.

DR. GOODMAN: That sounds about like one point four to me okay? MS. ELLIS: And also what we need everyone to do is to state your score. Each individual person please.

DR. GOODMAN: Starting with Dr. Phurrough?

MS. ELLIS: Starting with Dr. Phurrough.

DR. GOODMAN: Let's get the scores out and then when we're done with the scores I'll ask for any other points to be made.

DR. PHURROUGH: I voted one.

DR. GOODMAN: We have to speak into the microphone because we have the background noise.

DR. PHURROUGH: I voted one.

MS. CABRAL-DANIELS: Rene Cabral-Daniels, one.

DR. HESELTINE: Peter Heseltine, two.

DR. JANOWITZ: Warren Janowitz, one.

DR. MCDONOUGH: Bob McDonough, one.

DR. SAADI: I actually voted three, but can I make a quick comment?

DR. GOODMAN: No, you can in a few minutes, we need every score first.

DR. SAADI: I might have done it wrong so that's why.

MR. SAMSON: David Samson, one.

DR. STEINBROOK: Robert Steinbrook, one.

DR. SEAL: Of course on paper, Brian Seal, one.

DR. RUDY: Also on paper, Yoram Rudy, one.

DR. GOODMAN: Dr. Saadi, sounds like you voted 3 so even if you reversed it you'd still be in the same place. What was your comment Dr. Saadi?

DR. SAADI: I did not understand,

I'm assuming that these patients did not have EKG or they had EKG?

DR. GOODMAN: They were defined as --

DR. SAADI: It's not a screening test.

DR. GOODMAN: I wish you had asked that before, which is what your responsibility was. Patients who are asymptomatic, patients at risk for the disease. Take it as you will.

DR. SAADI: Okay.

DR. GOODMAN: Okay. So it was 1.374, was the score and that has implications for whether or not we're going to ask a subsequent question.

Let's now move to Question 1b, which is reliably and accurately detect coronary artery disease in patients with signs and symptoms suggestive of ACS with or without chest pain. And just to remind you and low to intermediate risk, was part of the definition. Dr. McDonough?

DR. MCDONOUGH: Just a quick clarification that second question. So the second question is whether it can detect, not whether it can detect better than anything else?

DR. GOODMAN: Correct, that was the gist of Dr. Steinbrook's question and clarification. There's no explicit comparator here. Thank you for that. Our TA people would you care to please provide your synopsis on 1b?

DR. COEYTAUX: Yes, we identified 11 studies that were eligible for and pertinent to 1b. One of them compared one of the technologies to coronary angiography for the detection of coronary disease. And ten of them used biomarkers as the criteria and standard for detecting myocardial infarct, MI.

DR. GOODMAN: And did you want to tell us anything about the quality of those studies. Remember this was the adequacy of the evidence, not just counting studies.

DR. COEYTAUX: The largest trial that was conducted largely in the United States was the OCCULT trial, which was one of the ten that looked at the detection, the ability of the prime ECG to detect acute MI was a good quality study, followed the others with fair quality studies.

DR. GOODMAN: Sorry to keep pressing. A good quality study comprised what in this case?

DR. COEYTAUX: Good quality study would require a adequate criteria and standard. In this case we considered the study adjudicated diagnosis of acute MI as determined by the end of the hospital stay.

So that there was a panel of experts that determined that the diagnosis was correct. So that qualified as a good quality study.

That there was a minimum amount of bias, avoiding bias by not having test result of one test inform the interpretation of

another test.

And having adequate recording of the methods, the patient population and the outcomes. Those are three of the more important criteria that go into the quality rating.

DR. GOODMAN: Good, thank you very much.

DR. COEYTAUX: You're welcome.

DR. GOODMAN: Are there any on point specific comments from any of our speakers on the matter of 1b. Dr. Strobeck?

DR. STROBECK: Thank you. This question I think details the sweet spot of the MCG trials, not only my trial, but the three studies that were done that resulted in four publications between 2000 and 2005.

These people were at intermediate risk, they had some signs and symptoms, they were otherwise considered candidates for coronary angiography. And the performance of this technology was very good in this group of

people.

DR. GOODMAN: Never the less though, none of those studies was detected in the technology assessment. Though we acknowledge that the study was published a few weeks ago that might have been relevant, correct?

DR. STROBECK: The three studies that were done prior were excluded according to the discussion because they were felt to represent patients who were in the catheterizating laboratory experiencing a controlled amount of ischemia and the result was detected by MCG.

That was incorrect. These trials were done prior to the cath lab, they were done on patients that were referred for coronary angiography and therefore I think should be included.

DR. GOODMAN: Thank you for your point of view, Dr. Strobeck. Any comments on behalf of our panelists? Yes, Mr. Samson.

MR. SAMSON: I think one of the points that the EPC raised was that by virtue of them be referred for coronary angiography they would be defined as high risk. Is that correct?

DR. GOODMAN: And we do care about low and intermediate, not high.

MR. SAMSON: Right and perhaps there was a mix of intermediate and high risk patients. But I would be curious if there were separate reporting of the results by risk category.

DR. STROBECK: This is Dr. Strobeck. The protocol specified in all three of those studies, that patients that had acute coronary syndrome, were in the throes of an acute myocardial infarction or had ST elevation were absolutely excluded from the analysis.

So those patients never were mixed in with the data. The only patients that were in that data set were patients that were

referred for coronary angiography. And on the day of the angiogram, they were totally stable, ready to undergo an elective procedure.

I can't see that those patients are considered high risk just because they're in a cath lab.

MR. SAMSON: My assumption is that the definition of risks are adhered to AHA guidelines, is that correct?

DR. GOODMAN: Dr. Strobeck, again.

DR. STROBECK: The AHA risk the Diamond Forrester scores and the Framingham scores all relate to a risk of a coronary event over a ten year period.

And intermediate risk goes anywhere from ten percent to 90 percent. So the patients and the incidents of coronary disease in the studies that we talked about was 41 percent, I think that's an intermediate risk.

DR. GOODMAN: Thank you. Dr.

Samson, are you satisfied at this point with this issue?

MR. SAMSON: Yes, it appears --

DR. GOODMAN: Okay. Let's have, Dr. Coeytaux, could you come in on that? Because we are, the matter at hand is exclusion versus inclusion fo certain studies.

DR. COEYTAUX: Yes, this is Dr. Coeytaux. Please correct me if I'm wrong, but at least one of the three studies that we had looked at and excluded stated specifically that all of the patients had known coronary artery disease.

In fact they had within six weeks. That's actually an important point, that we may be wrong, that I want to verify. We will take a moment to do that because my recollection from having read not long ago.

That at least one of the studies. They had, the patients had, known coronary artery disease and had been in the six within the six week period of having had a coronary

intervention.

So in our view these were patients with coronary artery disease and the closest classification given in the AHA guidelines is high risk, but they're with known risk. Known coronary artery disease, so that is the reason why we excluded them. That was my point.

DR. GOODMAN: Okay. Rather than kind of going back and forth on this does anyone have the study here?

DR. COEYTAUX: We do, and we'll get it in a moment.

DR. GOODMAN: Why don't you?

DR. COEYTAUX: Thank you.

DR. GOODMAN: It's worth taking a moment. If you could put your finger on that pretty soon that would be good. Go ahead, Mr. Samson.

MR. SAMSON: Assuming that this can get resolved, it appears to me that the -- one of the key concerns here is the results of the meta analysis, in which there is

sensitivity, specificity, pooled estimates for both prime body surface mapping and standard ECG.

What the meta analysis shows is higher sensitivity and slightly lower specificity. The confidence intervals overlapped between the two modalities and there's a great deal of heterogeneity.

What I take away from that is that it's difficult to reach a conclusion with that much heterogeneity and with overlapping confidence intervals.

And I would suspect that part of the uncertainty about the results is the fact that this technology has been evolving. I'm curious if it's going to get to a point of maturity and that it could be studies in, you know, larger studies. It's not a content area where there's a shortage of study participants.

DR. GOODMAN: So you're looking at it not just at any particular study, you're

looking at the meta analysis of the available evidence. You're finding A, a lot heterogeneity and B, overlapping confidence intervals for the group of studies.

And you're also suggesting that the addition of any one more study might not kind of sway that entire body of findings of the meta analysis?

MR. SAMSON: Right, I would be very interested to see large studies. Comparative studies, perhaps not limited to diagnostic accuracy but also to health outcomes.

Even though this particular question really deals with diagnostic accuracy.

DR. GOODMAN: Good, thanks. That something of which you may want to remind us when we look at evidence gaps later on. But thank you for raising it now, it is relevant to this question. Dr. Coeytaux, have you had a chance to take a look at that?

DR. COEYTAUX: Yes.

DR. GOODMAN: Anything you would like to report?

DR. COEYTAUX: I would, please. So we are talking about three studies all of which are unique studies. So they aren't exactly the same on populations.

DR. GOODMAN: Please speak right into the microphone for the panel to hear.

DR. COEYTAUX: Yes. So one study published in 2008 by Dr. Grube, the patient population, and I'll quote from the study.

"These patients represented a convenient sample in that each patient was already scheduled for coronary angiography for any indication. And had undergone at least one coronary vascularization procedure. At least six weeks before the scheduled angiography."

So they had already undergone a procedure.

DR. GOODMAN: That was an and not

an or?

DR. COEYTAUX: That's an and. Now there is one, another study here that excluded patients had had a previous vascularization.

But then another reason why we consider this group to be representative of a largely high risk is because they mentioned the number of patients who had a known history of myocardial infarction.

So the second study, also by Dr. Grube, published in 2007, of 562 patients, who were scheduled for coronary angiography, 44 patients, looks like about maybe 8 percent. And I'm doing that in my head.

Had a history of myocardial infarction more than six weeks prior to angiography. And no patients presented with acute coronary syndrome at the time of the study.

So the first one that I just mentioned we clearly would have excluded because they had a known diagnosis of coronary

artery disease. Well, actually that's not necessarily true. They had had previous vascular coronary interventions. And therefore high risk in our view.

And then the other one there was a proportion of patients who had known MI and also were excluded if they had acute coronary syndrome.

So we struggled with these studies, we had included them in the first report and we wanted to make use of this important information.

But no matter how we looked at it we concluded that for the purpose of this, these key questions, that these patients did not in our view represent the patients that are under consideration now with Question 1b, in our view.

DR. GOODMAN: Okay. Thank you, Dr. Coeytaux. Mr. Samson, does this sound in line with what you were thinking?

MR. SAMSON: Well, this gets at

the issue of the size of the body of evidence. And so according to BPC, they're not interested in expanding it.

DR. GOODMAN: Okay. Let's proceed to vote then. Does anybody have any very important information that is directly relevant to this question that we have not considered? Directly relevant on this point?

All right. Let's proceed to vote then. This is Question 1b. And we're looking at adequacy of evidence again, correct?

How confident are you that there's adequate evidence to determine whether or not SAECG technologies, any of them, are able to reliable and accurately detect B, coronary artery disease in patients with signs and symptoms suggestive of ACS with or without chest pain and low to intermediate risk.

One is low confidence, five is high confidence, three is intermediate.

MS. ELLIS: We have six of eight.

DR. GOODMAN: All right. I see

what, 2.625. Thank you. All right. So those are Questions 1a and b. Based on those findings and with our kind of rule about exceeding a mean vote of two and a half. We'll dispense with Question 2a. But we'll pursue Question 2b. We'll pursue Question 2b.

Were there any comments before we proceed? Dr. Steinbrook?

DR. STEINBROOK: Is there a vote?

MS. ELLIS: Yes.

DR. GOODMAN: Thank you for reminding me. Dr. Phurrough?

DR. PHURROUGH: Steve Phurrough, three.

MS. CABRAL-DANIELS: Rene Cabral-Daniels, one.

DR. HESELTINE: Peter Heseltine, three.

DR. JANOWITZ: Warren Janowitz, three.

DR. MCDONOUGH: Bob McDonough,

four.

DR. SAADI: Ryan Saadi, three.

MR. SAMSON: David Samson, one.

DR. STEINBROOK: Robert Steinbrook, three.

DR. SEAL: Brian Seal, three.

DR. RUDY: Yoram Rudy, three.

MS. ELLIS: Thank you.

DR. GOODMAN: Thank you. Any final comments before we proceed? Any explanation you want at all for a point for the agency to recall when it revisits this? Okay. Seeing none.

All right. We're going to proceed now to Question 2b, having skipped 2a. Now rather than the adequacy of evidence, we're going to talk about what the evidence tells us.

And so the wording in Question 2b is as follows. If the result of Question 1 is at least intermediate, which it is for Question b, in any of the conditions noted,

again that's B, how confident are you that ECG based signal analysis technologies are able to reliably and accurately detect, B, coronary artery disease in patients with signs and symptoms suggestive of ACS with or without chest pain. In low to intermediate risk.

And again, as we established earlier, we're not looking at a particular comparator. So if I can call the gentleman from the EPC up once again. If you would address briefly your findings and indicates for 2b?

DR. COEYTAUX: This is Remy Coeytaux, we found 11 studies that evaluated the performance of two devices. All of the patients that were equated in these studies fit under the category of patients with signs and symptoms suggestive of ACS with or without chest pain.

The results, I believe you're looking for results?

DR. GOODMAN: Yes.

DR. COEYTAUX: So the results are that there was, one of the devices is the LP 3000 system, a signal averaging device. And there was not a statistical significant improvement. But it's not a comparator.

There was sensitivity of 68 percent, I'm sorry I don't have that on top of my head. There is evidence of sensitivity for this device compared to coronary catheterization for the diagnosis of coronary artery disease.

And then there are another ten studies that evaluated the prime ECG to detect myocardial infarction. And a meta analysis with a fair degree of, large degree of heterogeneity came up with an estimate, a point estimate for both the sensitivity and the specificity of the prime EKG.

And I'm afraid I don't know those numbers off the top of my head.

DR. GOODMAN: Mr. Leisy has something.

DR. COEYTAUX: Yes, thank you. I'll come prepared with a report next time I'm up here. The meta analysis of eight of the ten studies and they did not explain why two are excluded. They were excluded, because one was a very small sample size and seemed to have changed the result in a way that did not appear to be representative.

And another one, clearly was a very early study that explicitly used a different algorithm for the prime ECG. And so we excluded that study as well. Although we also did an overall meta analysis that had very similar results.

But we felt the more robust meta analysis, the in the report that included eight studies, and they found that the sensitivity of the prime ECG for the diagnosis of acute myocardial infarction was 71 percent, 95 percent confidence interval of 46 to 88.

And that the specificity was 90 percent with a 95 percent confidence interval

of ranging from 83 to 94.

DR. GOODMAN: In the case of the first, the LP3000, that was where there was one study? What did you say about the confidence interval?

DR. COEYTAUX: I didn't mention the confidence interval. We don't have it on our slides, I can take a moment to find it here.

What I know is it is not statistically significantly different from the ECG. But I think right now we're not looking at a comparator. I will try to find an answer, would you like the confidence interval around that?

DR. GOODMAN: I thought you had said earlier it was broad.

DR. COEYTAUX: I didn't have it in my presentation and I don't have it in my head what the confidence interval for that study is. We didn't present that.

DR. GOODMAN: All right. I'm

sorry.

DR. COEYTAUX: I'm sorry we didn't have the, I imagine it's in here, and I can find it if you like.

DR. GOODMAN: The particular finding that you reported though was versus something was not statistically significant?

DR. COEYTAUX: Yes, so the study was designed to estimate the sensitivity and specificity of the index test. The LP3000 with coronary catheterization as the gold standard.

They also did the same for the EKG and our comment was that there was a higher estimate for the sensitivity of the test device, but that was not statistically significantly greater than the point estimate for the EKG.

But the sensitivities were the same for both those tests.

DR. GOODMAN: Good, thank you very much.

DR. COEYTAUX: The specificity was the same.

DR. GOODMAN: The specificity. Okay. Any questions or comments on the part of the panel for 2b? For 2b, this is what the evidence is saying about the findings. Does any speaker have any on point issue to raise with this question? Okay. We're going to get a clarification from Dr. Coeytaux.

DR. COEYTAUX: I very much apologize. I now have the report in front of me this is referring to the single study of the LP3000 signal averaging system.

And I significantly misspoke. I'm going to read from the report here. "The improved sensitivity of signal averaging ECG relative to the 12-lead ECG was statistically significant at the P level of .01.

DR. GOODMAN: Okay.

DR. COEYTAUX: So that is in contradiction to what I previously said.

DR. GOODMAN: Good, the record is

corrected, thank you very much. I'm glad that you stayed on top of that. Yes, Dr. Imhoff? This is Dr. Imhoff.

DR. IMHOFF: I would like to make a general comment on this process.

DR. GOODMAN: Dr. Imhoff, I hope your general comment has something at least vaguely to do with this question.

DR. IMHOFF: With this question and the previous question.

DR. GOODMAN: Go right ahead.

DR. IMHOFF: I'm slightly concerned as a scientist and as a researcher and also statistician that you're basing your vote on incomplete evidence. As we already had some unresolved discussions points with the TA report.

My impression is that the TA report is the major basis of your voting process and I doubt the scientific validity of that process. A little bit concerned. That's the only comment I want to make.

DR. GOODMAN: Thank you Dr. Imhoff, if you or anybody else has a particular reason to disagree with the TA we'd be glad to hear it briefly today, or in writing later on. Thus far I've heard none.

And so far as for particular reason, if there's particular thing that you thought was done inappropriately we'd like to hear it. We pursued the matters of definitions of these terms a few times.

We pursued the matter of a study that was published a few weeks ago with regard with what we could conclude or not conclude from it. Which I think is quite generous on the part of the process.

So your point is heard, I don't know that you can back it up at this point just yet however. So, Dr. Shen?

DR. SHEN: The largest studies that were conducted.

DR. GOODMAN: Into the microphone, please.

DR. SHEN: The three major studies that were conducted actually the focus was on people who have intermediate risks. Unfortunately there were patients with myocardial infarct which was about 8 percent for the large size study, about 500 patients.

And that, if we excluded those patients with the myocardial infarct, 8 percent of the study the sensitivity and specificity don't change.

So if you look at largely that the study that was conducted, in general under Dr. Grube and also the Hosokawa on this study were conducted in Asia.

And all of these studies of patients as well as the patients that we studied in North America, they are all considered intermediate. We look at risk factors or look at the post pretest of probability and your graphic data, so about 41 percent.

DR. GOODMAN: Thank you, Dr. Shen,

we did read directly from the published reports with regard to who was included and who wasn't. So what the study said is a matter of record.

Any further comments or questions on 2b, from panelists? From any of our speakers, anything in particular on 2b you'd like to add? No, okay. Yes, Dr. Seal.

DR. SEAL: They said there were three studies, I heard two, was there a third study as well? What was the other study that you mentioned?

DR. GOODMAN: Dr. Shen, if you have an answer you've got to approach the microphone.

DR. SHEN: Yes, one study was conducted in Westchester County Medical Center under Dr. Weiss. The largest study was in Germany under Dr. Grube, and then more intensive study conducted in Asia. Which was also a pretty sizable study.

DR. GOODMAN: Thank you. Any

further comments? Okay. 2b, let's vote on that. How confident are you that ECG based signal analysis technologies, could be at least one, are able to reliably and accurately detect coronary artery disease in patients with signs or symptoms suggestive of ACS with or without chest pain in low to intermediate risk.

One, low confidence, three intermediate confidence, five high confidence. Please press your buttons.

MS. ELLIS: All the votes are in.

DR. GOODMAN: Okay. Is that a 2.626

MS. ELLIS: 2.625.

DR. GOODMAN: Thank you very much. Any further comments before we go to the next question. Dr. Phurrough. Oh we need to hear all the votes, yes. Dr. Phurrough.

DR. PHURROUGH: Steve Phurrough, two.

MS. CABRAL-DANIELS: Rene

Cabral-Daniels, three.

DR. HESELTINE: Peter Heseltine, four.

DR. JANOWITZ: Warren Janowitz, three.

DR. MCDONOUGH: Bob McDonough, two.

DR. SAADI: Ryan Saadi, three.

MR. SAMSON: David Samson, two.

DR. STEINBROOK: Bob Steinbrook, two.

DR. SEAL: Brian Seal, three.

DR. RUDY: Yoram Rudy, three.

DR. GOODMAN: Okay. All those have been recorded?

MS. ELLIS: Yes.

DR. GOODMAN: Thank you, Ms. Ellis. All right. Let's proceed now to Question 3. And once again because we didn't address in question 2a because we had a low score in 1a. Then if I'm not mistaken we will not address 3a in this instance but we will

address 3b. I believe that's correct, Dr. Rollins, right?

DR. ROLLINS: Right.

DR. GOODMAN: So we're not going to do 3a, we're going to address 3b here. This is another matter of adequacy of evidence.

And in four we'll get to what the evidence might say. If we could have our technology assessment duo provide a synopsis of what pertains to 3b, what evidence pertains to 3b.

This is improves decision making. And I'll say it again. How confident are you that there is adequate evidence to determine whether or not the incremental information, incremental information, obtained from SAECG technologies beyond that provided by the standard 12-lead ECG, improves physician decision making in the management of coronary artery disease in patients with signs and symptoms suggestive of ACS with or without

chest pain.

DR. COEYTAUX: This is Remy Coeytaux, we did not find any studies that met our inclusion criteria that were designed to answer this question or really did provide a clear evidence in support of the question about providing -- having an effect on physician decision making.

DR. GOODMAN: Okay. Thank you. Any of our speakers have anything of substance to add to this particular question? Yes, Dr. Strobeck.

DR. STROBECK: Yes, thank you. I'm just curious for my own edification, what is the bar, where is the bar set for a diagnostic test that's probably twice as accurate as SPECT MPI, at detecting coronary disease.

When you have a very accurate test that way, what other evidentiary information do you need to show that it would affect physician behavior?

It seems intuitive that a physician is going to gravitate towards the most accurate diagnostic tests.

DR. GOODMAN: Yes, thank you for your question Dr. Strobeck. In fact intuition often does not play out in practice, as I'm sure you know.

There are many tests that are highly sensitive specific positive/negative predictive value. They may be blood tests, they may be imaging, genetic tests, what have you.

And the presents of even highly accurate information is often not found to affect a clinician's decision. So what we're looking for here, and this is documented CMS documentation by the coverage analysis group.

You'll find it documented in evidence appraisal guidelines by the major medical professional societies. That we're looking for some evidence, not intuition, that somebody's mind was changed by the

availability of this information on a test.

So its got to go beyond it's obvious, has somebody actually followed a group of physicians in making a decision or could infer sometimes from changes in utilization. That would appear to be a causal arising from having had a test in particular.

I appreciate your asking the question. Any further comments on the part of our panel or anyone else?

By the way, while our panel is thinking about how it's going to vote here, I'll just add for Dr. Strobeck and others. One of these to look for in the literature.

It's sometimes called an analytical frameworks, or causal pathways that lay out left to right. A population at risk on the left side of the page and at the far right side of the page is a box that will say treatment decision.

And further to the right of that

is outcome. And along the way we want to see that steps that get you from a test a result to a decision to change in outcome. So those are part of the standard analytical frameworks.

Okay. I see no hands raised for 3b, so let's go ahead and answer Question 3b again, this is an adequacy question. How confident are you that there is adequate evidence to determine whether or not the incremental information obtained from SAECG technologies beyond that provided by the standard 12-lead ECG.

So we've got a comparator here. Looking for marginal difference I should say. Improves physician decision making in the management of coronary artery disease in patients with signs/symptoms suggestive of ACS with or without chest pain.

And please do vote. One's low, three is intermediate, five is high. And again I apologize for rereading the question.

We want to do that for the record and just to remind everybody where we are.

MS. ELLIS: 1.125.

DR. GOODMAN: Okay. So all votes are in, and Ms. Ellis reports that is 1.125. I don't know that we need all the significant figures but that's what the map says, so thank you. 1.125 that would not meet the threshold of 2.5 which would take us to the next question. But let's get everybody's vote verbally, Dr. Phurrough.

DR. PHURROUGH: Steve Phurrough, one.

MS. CABRAL-DANIELS: Rene Cabral-Daniels, one.

DR. HESELTINE: Peter Heseltine, one.

DR. JANOWITZ: Warren Janowitz, two.

DR. MCDONOUGH: Bob McDonough, one.

DR. SAADI: Ryan Saadi, one.

MR. SAMSON: David Samson, one.

DR. STEINBROOK: Robert Steinbrook, one.

DR. SEAL: Brian Seal, two.

DR. RUDY: Yoram Rudy, one.

DR. GOODMAN: Thank you very much. Given the mean score here, we won't pursue Question 4 is that correct, Dr. Rollins?

DR. ROLLINS: Right, yes.

DR. GOODMAN: Okay, we won't do that then. Does anybody want to make any comments, any panelists want to make any comments about our findings for Question 3 at all? Before we proceed I just want to make sure we've got this covered.

All right. Then let's proceed to Question 5. Five and six are paired as have been our previous two pairs here. This has to do with adequacy of evidence. This is with regard to that incremental information obtained from the SAECG technologies that once again, beyond the standard 12-lead ECG.

But this time we're talking about eliminating the need for at the level of an individual patient, not across the population. Can eliminate the need for any of those four following technologies.

And Dr. Rollins and Dr. Miller, I guess we want to look at these individually do we? Or any? Dr. Phurrough? Individually?

DR. PHURROUGH: I think, because they're going to be different, they could be different.

DR. GOODMAN: Okay. So of the three, yes, A, B, and C. So we're going to need to do respond to all three of these. Our TA team, would you care to come to the microphone and tell us what you can about your findings for these.

DR. COEYTAUX: Would you like me to summerize for all three? Or one at a time? How would you like me to do that?

DR. GOODMAN: Let's do one at a time. Let's just kind of keep our train of

thought together here. I know that's going to take a lot of standing up and down, but please proceed.

DR. COEYTAUX: That's fine, very good. So this is about adequacy of information, for 5a, diagnostic laboratory testing. We identified 11 studies that looked at the devices, ten of those studies, incorporated the use of biomarkers for as a criterion standard for the diagnosis of MI.

One of these studies was a good quality study. Which was the large OCCULT study. And the outcome of that study was to determine whether or not there was a acute myocardial infarction that included biomarkers.

But they also included additional information that was obtained over the course of the hospitalization.

But the other studies in that's done with the prime ECG used biomarkers, CK, MB levels specifically as the criterion

standard. And those were all fair quality studies.

DR. GOODMAN: Fair, and what's above and below fair?

DR. COEYTAUX: There are three quality ratings. There's poor, fair and good. And poor is, we would rate a quality poor if there is evidence of, a high likelihood of bias being introduced for a number of reasons.

Or very poor reporting so that we couldn't assess the degree of bias. None of the studies were rated as poor.

Fair quality studies are ones that have a moderate risk of bias. In the design and the conduct of the study, or the reporting may not be quite sufficient enough to give us confidence that there isn't such bias. And that was on most of the studies.

The main reason for rating a quality poor was the incomplete criterion standard, in this case, which was the very question we looking at. Which was the

biomarkers which we considered not a complete, fully adequate criterion standard, and therefore just that would bring the quality down from good to poor.

DR. GOODMAN: Thank you. Again we're going to have to do these one at a time. Panel, any question about A, diagnostic laboratory testing, for example troponin? Dr. Steinbrook.

DR. STEINBROOK: It's really a comment about the common wordage under five. That we're presupposing incremental information obtained from the SAECG technology beyond that provided by the standard ECG.

And then we go on to A, B, and C. But the way I look at this is that for the one device that had most of the studies my recollection is that the confidence intervals for the difference in the sensitivity between ECG and SAECG overlapped.

And then you have one study, one study of the other device, the LP3000 and

while in that situation the LP3000 was more sensitive than the ECG with the P, less than .01. If you actually go back and look at the numbers it one study and you've got a universe of 108 and it's 75 versus 60 which is driving the .01.

So those numbers are the numbers and that's it. There's no other evidence beyond that. So I'm just talking about the first part of this before we get into A, B and C.

DR. GOODMAN: Okay. So do you propose that we look at it any differently or just?

DR. STEINBROOK: No, but I think the common part five, at least the way I approached this, drive some of my thinking before I even get to these other things down below.

DR. GOODMAN: Okay. Comments by any of the other panelists on interpreting this? I think we've got to take it literally

unless somebody pushes us off that definition. Okay. Any comments from one of our speakers, on the matter of diagnostic laboratory testing. Yes, this is Dr. Beker.

DR. BEKER: This is actually a question about the wording of Question Number 5 and the wording "eliminate the need" at the level of an individual patient.

I just wanted to ask the authors of these questions whether the intention was actually, eliminate the need is quite an extreme term. So was the intention, reduce the need, we know that some of the technologies reduce unnecessary further procedures.

DR. GOODMAN: Dr. Miller is approaching the microphone.

DR. MILLER: I think that you could perhaps say it would, that the SAECG technology would substitute for, so yes, we are talking about totally eliminating the test, either A, B, or C.

DR. GOODMAN: There would be no need for, given this incremental information if it is available?

DR. MILLER: Yes, correct.

DR. GOODMAN: Okay. That was the intention, thank you.

DR. PHURROUGH: For an individual patient, right?

DR. MILLER: Yes.

DR. GOODMAN: Right. And that's an important point, and it's explicit in the question this is not a population, cross population, finding. Dr. Rollins?

DR. ROLLINS: I'd just like to make a quick comment. When we posed, A, diagnostic laboratory testing, troponin. We were making the assumption that this test could detect myocardial ischemia.

Based on this mornings conversation it was pointed out that myocardial necrosis was made from troponin diagnosis.

DR. MILLER: To clarify what we were thinking, the difference between unstable angina and a NSTEMI is whether or not you have a positive biomarker or positive troponin. So that was the thought process behind this question. That instead of using a biomarker to make that distinction, that you could use an SAECG technology.

DR. GOODMAN: Thank you both. Okay. Further points to be made with regard to diagnostical laboratory testing for example troponin, in this one?

Okay. Let's call the question again, this is an adequacy of evidence question now, and adequacy of evidence question.

How confident are you that there is adequate evidence to determine whether or not the incremental information obtained from SAECG technologies, beyond that provided by the standard 12-lead ECG, can eliminate the need.

And you heard what that meant, at the level of an individual patient, you heard that was well. For diagnostic laboratory testing of for example, troponin. Scale of one to five, one low confidence, three intermediate, five, high. Adequacy of evidence.

There it is, I see a vote of 1.5 as a mean. Dr. Phurrough, your score?

DR. PHURROUGH: Steve Phurrough, four.

MS. CABRAL-DANIELS: Rene Cabral-Daniels, two.

DR. HESELTINE: Peter Heseltine, one.

DR. JANOWITZ: Warren Janowitz, one.

DR. MCDONOUGH: Bob McDonough, one.

DR. SAADI: Ryan Saadi, one.

MR. SAMSON: David Samson, one.

DR. STEINBROOK: Robert

Steinbrook, one.

DR. SEAL: Brian Seal, one.

DR. RUDY: Yoram Rudy, one.

DR. GOODMAN: Thank you all. 1.5, that will mean that we won't pursue this matter in the subsequent question in what the evidence tells us.

Lets proceed to 5b. The question is the same. This time it's with regard to the need for noninvasive tests, noninvasive tests of cardiac anatomy functioning, example, stress testing, echocardiography.

These are noninvasive tests, we'll get to invasive next. Yes, Dr. Coeytaux on this matter of noninvasive testing?

DR. COEYTAUX: We did not find any included studies, eligible studies that address this question.

DR. GOODMAN: No studies. Thank you. Do our speakers have anything to suggest or assert on this? Dr. Strobeck, yes, sir?

DR. STROBECK: I would only ask

the panel to consider the trial that we presented today. Which was the noninvasive comparison of SA technology to SPECT MPI and showed that the SA technology did very well.

DR. GOODMAN: Okay. Thank you, and this was the October 2011 study, it was too recent to be entered here?

DR. STROBECK: That's correct.

DR. GOODMAN: Thank you for raising that. Any questions on the part of our panel? Panel we can only deal with the evidence that's in front us but again I can't tell you to not regard anything else you might have heard. That's quite fine, that's up to you.

All right. Would you please vote then on a scale of one to five, with regard to these noninvasive tests. This is an adequacy of evidence issue, incremental information eliminate the need for noninvasive tests.

The score is posted, it is 1.25, Dr. Phurrough, your score?

DR. PHURROUGH: Steve Phurrough, two.

MS. CABRAL-DANIELS: Rene Cabral-Daniels, one.

DR. HESELTINE: Peter Heseltine, two.

DR. JANOWITZ: Warren Janowitz, one.

DR. MCDONOUGH: Bob McDonough, one.

DR. SAADI: Ryan Saadi, one.

MR. SAMSON: David Samson, one.

DR. STEINBROOK: Robert Steinbrook, one.

DR. SEAL: Brian Seal, two.

DR. RUDY: Yoram Rudy, one.

DR. GOODMAN: Thank you all. Any closing comments on that one? No, then let's proceed to 5c, same question but the matter this time with regard to eliminating the need is invasive tests, invasive test of cardiac anatomy or functioning, for example, coronary

angiography.

And again this is an adequacy of evidence question, incremental information obtained from the SAECG beyond that provided by the standard 12-lead ECG, eliminating need at the level of individual patient for invasive tests of cardiac anatomy for functioning.

Please do vote. Enter your vote. Got three more coming. All votes are in, I see 1.375. Dr. Phurrough, your vote?

DR. PHURROUGH: Steve Phurrough, four.

MS. CABRAL-DANIELS: Rene Cabral-Daniels, one.

DR. HESELTINE: Peter Heseltine, one.

DR. JANOWITZ: Warren Janowitz, one.

DR. MCDONOUGH: Bob McDonough, one.

DR. SAADI: Ryan Saadi, one.

MR. SAMSON: David Samson, one.

DR. STEINBROOK: Robert Steinbrook, one.

DR. SEAL: Brian Seal, two.

DR. RUDY: Yoram Rudy, two.

DR. GOODMAN: Thank you all. Any explanatory or closing comments on this issue? Dr. Phurrough.

DR. PHURROUGH: Since I was a significant outlier on A and C I thought that I would explain. I think there is sufficient information for us to recognize that these technologies are not intended to replace either a diagnostic test for an MRI, the troponins or angiography.

I think we have enough information to recognize that they're not intended to replace that. We don't have enough information to determine whether they should replace some of these other noninvasive tests. So that's that's why I voted four, I think we can make the determination, they are not

intended to replace those.

DR. GOODMAN: Good, thanks for that clarification, very helpful and I think the agency will find that enlightening. Thank you. Yes, Dr. Strobeck. I find your comments usually enlightening, Dr. Phurrough.

DR. STROBECK: Yes, and I totally agree with Dr. Phurrough, these technologies, I think can replace or at least change the decision to do an invasive test on a patient by patient basis.

Not across the board, it's not going to replace coronary angiography. But on a given patient with a low score, that patient may not need an angiogram. It's going to save a lot of unnecessary angiograms.

DR. GOODMAN: Good, thank you, Dr. Strobeck, your point is well taken.

All right. Then we would proceed to Question 6, however the criterion for pursuing Question 6 involves the average score of the parts of five A, B, and C, none of

which achieved the threshold of 2.5. Therefore we'll need to proceed to the next question. Any other comments before we start Question 7, which deals with patient outcomes. Any comment on five or six, in addition to Dr. Phurrough's? Dr. Saadi, yes? Directly into the microphone.

DR. SAADI: Will you clarify the definition of outcomes for all of us?

DR. GOODMAN: I'd be glad to. And all I have to do is read what's on front of me. On the first page of the preamble is Paragraph 4, and it says health outcomes of greatest interest.

Health outcomes of greatest interest include mortality, MI, that's myocardial infarction, cardiac function and quality of life. Those are health outcomes.

If I might add health outcomes typically do not include biomarkers or what are often called intermediate end points. These are things that happen to patients,

things that patients can feel usually. Mortality, Myocardial infarction, cardiac function and quality of life.

I will add just for the record, Dr. Saadi, that in some cases certain biomarkers have been validated repeatedly as being highly associated with or highly predictive of health outcomes such as these.

And of those instances one might therefore use such a surrogate. So it is possible that some biomarkers do indeed substitute very well for health outcome.

It's your judgement to decide whether or not that applies in this case. But just clarifies the definition. Thank you.

Okay. If we could have Dr. Coeytaux approach the mic as we're going to lay out Question 7. This has to do with adequacy of evidence again, not what evidence says, adequacy of evidence regarding whether or not the use of SAECG technologies significantly improves patient health

outcomes.

So points of clarification, SAECG technologies doesn't have to be all of them, will take any of them. Not just improve patient health outcomes as defined a moment ago, but significantly improves them. Would you care to comment on Question 7, Dr. Coeytaux?

DR. COEYTAUX: Yes, in our report we state that there were two studies that provided some information that may relate to this question. One of the studies did not actually publish or report the data. So about outcomes so it really isn't helpful to this question.

The other study is a good quality study, it's this OCCULT trial that looked at the prime ECG. However it was not designed to answer this specific question. It is not designed to answer this specific question.

But at the very end of the results section they do comment that there were

differences in outcomes in terms of mortality based on the findings of the prime EKG compared to the findings of the standard ECG.

And if you'd like me to tell you those. It was an incidental finding saying that of the 225 patients. Hold on, I'll read it for you, I think it's helpful enough.

Two hundred twenty five patients were eliminated because of insufficient data or unevaluable ECG. And in the remaining 1,500 patients, the available outcome data on 80 lead reading of ST elevation, was associated with a statistically higher rate of death, with a high odds ratio of 11 range compensatable from 1.8 to 67. And a strong trend toward a higher rate of death and recurrent MI odds ratio, 3.4, than those of patients without a reading of ST elevation in the 80 lead. It's complicated, but I'll paraphrase it.

That they found that of the patients who -- I'm going to try to make this

clear, because it actually is complicated.

The patients who were identified with ST elevations by a prime ECG, had a higher rate of mortality compared to patients who didn't have that ST elevation. That was not found on the comparator of the standard EKG.

DR. GOODMAN: Okay, thank you. But tell me why -- maybe I'm missing the point. Tell me why that is causal as opposed to prognostic? It sounds prognostic as opposed to causal, correct?

DR. COEYTAUX: It isn't causal, first there's no, we cannot make a causal inference. And it may be that this data should not be discussed here. I really don't know.

The reason that we had brought it up was because one possible explanation is that there could be a causal connection in that. It's possible, we don't know.

It's possible that the results of

the prime ECG resulted in actions taken by the health care team that lead to changes in ultimate outcomes. That's possible but we don't know that.

DR. GOODMAN: Or could simply be that people who had certain test result using particular technology that you're more or less likely to die ultimately. Which may have had nothing to do with how you were treated.

DR. COEYTAUX: And that's absolutely true. And since we don't know this, I don't want to do the irresponsible thing by trying to create a causal relationship when there may not be there.

I'm reporting it because I at least look at that and said, "Hmm, that's an interesting finding, what could it mean?" It could mean just straight forward prognostic. Very high likelihood that it is.

But it could also be because of an actual impact on health outcomes. And we don't know.

DR. GOODMAN: Okay, I appreciate it. If anybody's got a shred of evidence or insight that says why that might be causal as opposed to prognostic I'd be really interested in hearing it. At least based on what I heard.

Comments from any of our panelists on this issue, patient outcomes, adequacy of evidence. Any of our speakers on this issue. Thank you, let's proceed to vote then.

This is Question 7, adequacy of evidence, how confident are you that there's adequate evidence to determine whether or not the use of SAECG technologies, any of them, significantly improves patient health outcomes.

And I'll remind you that patient health outcomes were defined in the preamble. One is low confidence, three is intermediate, five is high confidence.

Thank you. All votes are in the mean score is 1.125. Dr. Phurrough?

DR. PHURROUGH: Steve Phurrough, one.

MS. CABRAL-DANIELS: Rene Cabral-Daniels, one.

DR. HESELTINE: Peter Heseltine, two.

DR. JANOWITZ: Warren Janowitz, one.

DR. MCDONOUGH: Bob McDonough, one.

DR. SAADI: Ryan Saadi, one.

MR. SAMSON: David Samson, one.

DR. STEINBROOK: Robert Steinbrook, one.

DR. SEAL: Brian Seal, two.

MS. ELLIS: Dr. Rudy, two.

DR. GOODMAN: Thank you very much. Any comments on this one before we proceed? Because the mean score falls below the threshold we would not address Question 8.

But I don't want to leave this matter of patient outcomes unless, until

you've decided you've got nothing else to say about it. At this point, why you voted or anything like that. It seemed like a pretty uniform vote down the line. Dr. Rollins?

DR. ROLLINS: Does adding the words "lead to" make a difference in terms of trying to explain the causal relationship as opposed to the way it sort of seems.

Because somebody might say a diagnostic test in itself is not going to alter outcomes unless somebody uses the results of that to change management.

DR. HESELTINE: Clearly the diagnostic tests influence decision making but obviously don't have direct impact. So unfortunately when you say improves here, it would probably better to word that somewhat differently to imply the indirect benefit.

DR. GOODMAN: Let me just submit that various designs of studies, various well-designed studies, and not just in RCT can provide acceptably rigorous evidence, that

there's a causal effect. A causal impact of a diagnostic on a decision and sometimes even a patient health outcome.

So I think improves is certainly acceptable and feasible here, I think we all recognize that the improvement is not necessarily direct. But that doesn't mean it is not causal. So your point is well taken, Dr. Heseltine.

And Dr. Rollins, thank you very much, it's possible that it could have a cause indirectly. But we'd be glad to entertain any study that's designed to figure that out. Now that we saw that today. Dr. Steinbrook?

DR. STEINBROOK: In terms of the general subject area, you know, forgetting about the wording. But you would really want for adequate evidence a body of studies that were looking at health outcomes and collecting in these four different domains that you mentioned.

Whether they're perspective or

cohort, or what have you, in terms of study design. And that's, I think, what we would be looking for. It didn't seem at least in this instance that we just had a lot of information about how health outcomes related to this technology.

DR. GOODMAN: Right, thank you for your point. Well stated, Dr. Steinbrook. Yes, Dr. Cabal-Daniels.

MS. CABRAL-DANIELS: I'd like also to point out that when we talk about patient health outcomes here, I'm assuming the outcome as defined by the provider. And that we should also always bear in mind that a patient health outcome my be defined differently by the patient, him or herself.

DR. GOODMAN: Point well made Ms. Cabal-Daniels. And I would say that one of the aspects that we hope is useful about MEDCAC meetings such as this is to share. Not just among MEDCAC members and CMS staff but other stakeholders that.

The environment of expectations for evidence is changing. In general the bar is kind of rising but it's not just a slightly rising bar in some cases it's the nature of the evidence that's changing and patient reported outcomes.

Patient centered outcomes, are of increasing importance with regard to the evidence environment. So your point is very well taken and I would say that's a useful signal for those who have the job of validating innovations and other interventions. Thank you. Dr. Heseltine?

DR. HESELTINE: So to that point, follow on with it. One of the things which is as physicians we tend to look for a disease. Patients obviously want to be told they don't have disease.

So studies that are designed to actually show that the person doesn't have the disease, which is what patients want. These are extraordinarily valuable studies.

So some of these technologies studies might actually demonstrate that you don't have cardiovascular disease or you don't have coronary artery disease and that would be very, very helpful.

DR. GOODMAN: Rule outs are great, yes, Dr. Heseltine. Dr. Janowitz.

DR. JANOWITZ: On that same point, I think the point raised earlier that avoidance of more invasive studies is also a positive outcome that should be investigated. Or touted as almost as well as the avoidance of mortality.

DR. GOODMAN: Thank you very much. And when you kind of look at how you might detail patient orientated outcomes avoidance of invasive procedure may very well be highly preferred by patients. So point well made.

We've already obviously ventured into Question 9 without my having had to declare it. We've been listening to evidence since about 8:00 a.m. this morning.

And having gone through our voting questions, we'd very much appreciate if our panelists, and I hope something -- at least one thing from each panelists regarding gaps in evidence.

And the formal question is stated as, what evidence gaps exist in the field of signal analysis ECG devices?

The reason we're doing this is that, keep in mind that there's not a national coverage determination on the table. The agency is going to be looking at this obviously.

Otherwise there would not have been this MEDCAC meeting. It's very helpful to the agency as well as innovators and other stakeholders to understand whether there are evidence gaps that could be filled. That might provide greater guidance to the medicare program as well as to clinicians, patients, caregivers and family members.

So panel, what's missing here

that's a high priority for being filled with regard to evidence. Do I have a first taker? Dr. Seal.

DR. SEAL: Coming from a health outcomes background. The patient reported outcomes of symptoms and quality of life are really important in this patient population. It's one where there's a significant morbidity and mortality. So that becomes a high piece.

So to put some of those instruments into the trials would be helpful both to the physician and the patient when decision making around what the next test is.

DR. GOODMAN: Thank you, Dr. Seal, very helpful. Dr. McDonough is next.

DR. MCDONOUGH: Just the point that's made a lot of times today, how we were struck that a lot of these studies didn't have an appropriate reference standard. And that's something that we need in the future.

DR. GOODMAN: Thank you, reference standard, excellent point. Further points?

Mr. Samson?

MR. SAMSON: I think it's really important to figure out what the comparison ought to be. Is it some series of test and treat strategy, one of which includes signal average ECG and another that doesn't? Should it be head to head comparisons of diagnostic accuracy on things like SAECG and perfusion imaging. These things really need to be addressed.

DR. GOODMAN: Thank you, Mr. Samson. Next point, Dr. Heseltine.

DR. HESELTINE: The piece that I think is missing, that is relevant to all sorts of studies that we do in diagnostics, is to actually determine precisely what is the altered case management that will be done for this particular patient?

Even if it is subpopulation of patients. Because without that, all you have is, well I have interesting additional knowledge, or interesting additional academic

knowledge. Or maybe physiologic knowledge.

But really it's about altering the clinicians management of the patient. That's got to be end point for these studies.

DR. GOODMAN: Thank you, Dr. Heseltine. Ms. Cabral-Daniels.

MS. CABRAL-DANIELS: It's like to build on a number of points made. I hope that will be approached patients we don't look at them monolithically. But that we look at them with the level of sensitivity, that we have, in other areas.

DR. GOODMAN: Thank you. Dr. Steinbrook.

DR. STEINBROOK: I want to make a slightly different point. This follows up after a question I ask earlier about the FDA clearance of the devices which should be FDA cleared. And what information could be learned at that time.

There's a big debate in this country right now about the process for

getting medical devices on the market. There's been the ILM Report. And a lot of discussion.

But I would just submit for a group such as this and for Medicare, to the extent that there is clinically relevant data, which is generated as part of the process of getting devices on the market. And cleared by the FDA, it would really help in terms of figuring out how to use them.

DR. GOODMAN: That is a good point. Thank you, Dr. Steinbrook, very good. I believe Dr. Phurrough was next.

DR. PHURROUGH: Two or three things. First of all we had, in the TA identified, 11 technologies and we found studies on three. One on one study, three or four on MCG, and ten of various quality. Only one really decent one on the prime.

So the big evidence gap is, there's none, for most of these technologies. That's a gap that goes along with this FDA

clearance process, which says, you got to demonstrate that you can do something similar to something else, that had no evidence of it having any benefit. Not that I'm biased against that particular process.

Two, any evidence would be better than what we have in preventive devices.

Secondly, to go on with and expand on some of the other comments. Too much clinical study today focuses -- doesn't focus enough on the needs of some of the end users, like patients.

What do patients really want to know. What do peers really want to know? What does Medicare need know to make a decision? What does United need to know to make a decision? Focus is many times on what I need to know to get to the market? Which is a vastly different question.

So there's gaps in the kinds of information that patients and clinicians and payers need to know to answer those particular

questions.

There's an assumption commonly with many technologies that I need to meet the standard of the current standard of care. And that's a false assumption in today's climate.

Just because you have as much as or more evidence than the current standard of care, doesn't mean it's any good. And so, yes, new technology has a higher bar. Live with it. That's the way it is.

And then finally it's just the, you know, issue of diagnostics, it's just got to move beyond. You know the sensitivity, specificity, characteristics, those are just not adequate. Regardless of whether they exceed statistically or in other manner. Those of current technologies, you've got to demonstrate that your technology changes things.

Preferably changes patients outcomes. That is difficult and in some cases there are other studies that clearly

demonstrate that a particular intermediate outcome will in fact change the end outcomes that we're interested in.

But that's got to be a pretty clear process that's already developed. Any thinking that says I need to get my sensitivities specificity data and my characteristics, diagnostic characteristics data out there. And that's enough. That really is just insufficient in today's market.

DR. GOODMAN: Thank you, Dr. Phurrough. Dr. Saadi.

DR. SAADI: I was actually going to repeat, not as well as you actually you did, Dr Phurrough. That's actually our precise challenge here. That this an observation I would like to make this comment, for the record, this comment that the industry folks, and I'm part of it, as you know. That we actually have a different expectations from the FDA.

And it actually comes to CMS. Or

any peer globally. It's actually completely different. So the part actually I think is missing, that the industry folks, we don't quite see it. It's a very, we have a very clear understanding, we have in house experts. In terms of how to satisfy FDA.

And we actually have very limited understanding. How to satisfy any payer including the CMS, of course.

And now people like me are, and Dr. Harland, obviously you know that. But that's not actually enough. So I think that something in there, I think should be discussed here or at least addressed. Or CMS, you actually need to send the signal out, hey guys, listen, this is actually the new reality.

DR. GOODMAN: Thank you, Dr. Saadi. As I think I suggested earlier, I think that you're highlighting. Meetings like this help with that changing environment, make that changing environment explicit to the

innovators as well as others.

I would add that on occasion innovators can come to CMS for early meetings to discuss mutual evidence expectations. And those are often very helpful meetings.

Further points on evidence gaps, Dr. Phurrough.

DR. PHURROUGH: We've been sort of talking the researches and I'll turn around and talk to CMS a bit. Something that covers doesn't have an option really but because I've worked here long enough I can say what I think.

The real gap that researchers have is knowing what the bar is. You know, FDA fairly good at telling you what the bar is. CMS says we'll let you know what the bar is after we make out decision.

Which is pretty tough. We says we want adequate evidence, well what's adequate? I've lived with that, I recognize that there's challenges in doing that.

But they need to grow up. It's not a coverage issue, it's a CMS issue. Actually a department issue, of deciding that there needs to be some clearer guidance that says, here's what we expect for us, for you to bring to us, so that we can make a reasonable decision based upon that.

DR. GOODMAN: Thank you, Dr. Phurrough, with your view from the inside as well as the outside. Ms. Cabral-Daniels.

MS. CABRAL-DANIELS: I would like to piggy back on that with regard to enhanced transparency of the agency, not only benefits researchers, but I think it would help the patient population also.

DR. GOODMAN: Transparency. Thank you. Further comments on -- yes, Dr. Janowitz on evidence gaps.

DR. JANOWITZ: Yes. I think what has to be done in my view, is really focus on what this technology is potentially used for. I don't think it's ever going to replace

biomarkers. I don't think it's ever going to replace angiography.

But where it has a potential role is in this whole bunch of intermediate tests, which currently exist to determine which patients get referred on for further testing.

Any time you have four or five different competing modalities to determine, you know, the patient's next step. I think there's room for potentially developing a better test.

So if this technology could be better at determining who has to go on for more invasive procedures. I think that is a good niche for it. To try and make it do everything, it's just not going to happen.

DR. GOODMAN: Thank you, Dr. Janowitz. Further points on evidence gaps. Are there any of our speakers today who in a concise way would want to indicate or point to an evidence gap or comment regarding an evidence gap?

Just to capture your insights for the agency and others. Yes, Dr. Strobeck. Welcome back to the microphone.

DR. STROBECK: Thank you very much. No, I just really would like to echo the comments of Dr. Janowitz. I mean we need to focus on specific areas. And I think the area of highest importance, at least from my point of view as a practicing cardiologist, is really making evidentiary based decision on which diagnostic test to do.

Many patients are getting two or three diagnostic tests, because of the inaccuracy are being, essentially loaded with testing prior to the gold standard test, which they ultimately get anyway. And if we can have an accurate way of determining who needs that invasive strategy. I think that makes a big difference. That's what we're going to try to do. Bring back that kind of evidence base.

DR. GOODMAN: That's great. Thank

you very much, Dr. Strobeck. Yes, Dr. Imhoff.

DR. IMHOFF: Well it was mentioned somewhat before, but I would like to express that it is extremely important when we're talking about myocardial ischemia. We need to have an accepted gold standard for myocardial ischemia and not only for the morphological change and the morphological CADDC's.

And that is something where the panel or CMS or other agencies may make a strong recommendation what is considered a gold standard test for myocardial ischemia.

Because in the literature we also have the problem that it is very difficult to agree on that. Also for instance with the FDA, I had discussion recently.

DR. GOODMAN: Good, thank you for your comment Dr. Imhoff. Yes, gold standard for myocardial ischemia. Greater clarification. Yes, Mr. Leisy.

MR. LEISY: If I could just speak on behalf of one of our team members, Dr.

Galen Wagner, who's a specialist in electrocardiography and journal and editor for the journal for the electrocardiography, directed a lot of our discussion on the certain technologies and devices in there applicability today.

He spoke specifically about the body surface mapping device, which began development about ten or 15 years ago. Prior to this thought of spending the equivalent, which is only a very recent idea.

And he said his argument was that back when it was first designed a lot of the STEMI's, the ST elevation that they found were on the posterior leads. Which now the AHA has realized that ST depression on the anterior leads V1 through V4 would show ST elevation a posterior side.

And so he says that, perhaps some of the data could be skewed because they would accept. Because the body service mapping would increase ST elevation, based on the

STEMI equivalent criteria.

And I think the gap is that, is there another application for today's technology where you can use that information without developing any new devices.

DR. GOODMAN: Good. Thank, you.

MR. LEISY: You're welcome.

DR. GOODMAN: Sometimes you develop a device for purpose A and purpose B emerges. Thanks. Yes, Dr. Janowitz.

DR. JANOWITZ: Yes, I'd just like to make a couple of comments about the gold standard for perfusion. This is what I do everyday. If I had to say right now with the gold standard that we have available non-invasively would be cardiac PET. Next would be cardiac SPECT with attenuation correction.

And potentially in the future coronary CTA with non-invasive detection of fractional flow reserve, which is a study that's currently going on. So, you know, if

anyone else has any better ideas, I think that is where we are right now.

DR. GOODMAN: Great. Thank you. Okay. I think that's it for evidence gaps. We're not done actually. I'll try to simplify this. We have a final question that has to do with generalizable or external validity. I'll just ask you to kind of integrate under the curve here. We don't have to get granular about this.

But we've talked about a set of evidence questions that we've graded on a Likert scale. We talked about evidence gaps. It's important for the Medicare program to understand whether or not there is any differentiation between what you saw in the evidence and what might be applicable first to the Medicare population.

So did you see or hear anything today that raises a flag, or is a special consideration regarding how useful the evidence that is available is applicable in

particular to Medicare beneficiaries. That is the disabled and those, typically those disabled or greater than age 65.

Any points to be made about any differentiation there? Age, group, or disability? Dr. Phurrough.

DR. PHURROUGH: So if we say there's not adequate evidence to draw conclusions on most of these questions, can we even answer this question?

DR. GOODMAN: Well, thank you for posing that. It's possible that while the evidence overall was not adequate. It's possible that there might have been a bit of it that was directly relevant to Medicare population.

Or in the limited cases where we found adequate evidence, it was -- I think only one, that might have been more or less relevant to a Medicare patient.

The tone of your question, I agree with this. Not allowed it to go on in the

first place. So how can we conclude otherwise. But just wanted to provide the opportunity. So any additional bit on that, Dr. Phurrough?

DR. PHURROUGH: No.

DR. GOODMAN: Point well taken. Dr. McDonough.

DR. MCDONOUGH: I interpreted that question a little bit differently, I mean, in many cases you're concluding that you're uncertain and I just assume, and maybe I'm wrong, that to the extent that these studies might involve patients in the Medicare population. Your uncertainty would extend to them.

So you're confident or have some confidence that your conclusions about uncertainty would apply to the Medicare population as well.

DR. GOODMAN: That's also correct. And is there anything that you've seen that would go against that? About uncertainty.

We're uncertain about the body of evidence and therefore you're saying we --

DR. PHURROUGH: I don't, I mean a lot of these studies seem to be, in my opinion, you know, a lot of them look like in older populations that would be served by Medicare.

DR. GOODMAN: Yes. Dr. Heseltine, you've reversed, but go right ahead.

DR. HESELTINE: So the way I read that question is, are you confident that these conclusions, which are our answers to the questions. Are applicable or generalizable to the two populations in question.

DR. GOODMAN: Yes.

DR. HESELTINE: So the fact that we found the evidence wasn't enough in many cases. The question here is, am I confident that that conclusion, that there wasn't enough evidence, is applicable. And so I thought that was to be in the affirmative.

DR. GOODMAN: If the findings that

you made today, how confident are you that the findings were made today, apply to Medicare population? And if it's affirmative, that means that, yes, what we said in general applies to Medicare people.

DR. HESELTINE: Right. Because you could answer their question the other way and say, that negative we had insufficient result, therefore we have insufficient evidence for that population. So I just wanted to make sure.

DR. GOODMAN: No. Thank you for your interpretation. Let me ask for a clarification. I don't see a Likert scale on my scoring sheet for questions. And I thought it was a discussion question, and not a grading question. And typically in the past --

(Off microphone discussion)

DR. GOODMAN: One of the scoring sheets has it, one doesn't?

MS. ELLIS: Right. Well, the one

that you have is just the regular voting questions. But the one that the panel members have is the actual score sheet, because they actually vote.

DR. GOODMAN: Okay. So you would like a vote on this.

MS. ELLIS: Yes, we need to vote.

DR. GOODMAN: Okay. I apologize then. The ones I was looking at had scoring for everyone, but not this one. Okay. Panel, I apologize then. We do need to vote on this one.

MS. ELLIS: Yes.

DR. GOODMAN: Oh, my apologizes, it was not in front of me. Dr. Seal.

DR. SEAL: I'm hearing both ways. So one is saying that we're applying the evidence to this population. Most of the trials that I saw had 50 percent of the population was a Medicare population. Which is higher than a lot of the other trials in drug trials. Then most of the trials that I

saw that they had presented came from community centers.

So just the fact that they have the evidence, or at least it's not powered for that. But enough to show that this is where the patients came from, is important.

But I'm trying to decide how confident are you that these conclusions are generalizable too. How are we interpreting the question?

DR. GOODMAN: You've drawn some findings today or some conclusions today about adequacy of evidence, what the evidence says. Whether it was strong evidence or weak evidence, or if the evidence showed something or it didn't. How confident are you that, that set of findings applies in particular to the Medicare patient population?

And as you just pointed out, a lot of these studies probably did include Medicare eligible patients. So if you're highly confident that our findings today applied to

them, you'd say something like a four or five. If you weren't confident, if there was a big gap between the available evidence and what needs to be known about Medicare population, you'd probably score at the bottom of the scale.

DR. SEAL: Yes, my thought is that even if we scored say a lower number on one of the earlier questions, it still applies to this population.

DR. GOODMAN: Yes. Which means you'd be highly confident that perhaps inadequate evidence still applied here. That would push you to the top and the other instance it would push you toward the bottom.

Thank you. Dr. Phurrough.

DR. PHURROUGH: So the conclusions are the panels conclusions. Not the conclusions of the research that we have reviewed? It's the evidence that we've reviewed.

DR. GOODMAN: Correct. How

confident are you? Correct. All right, so once again, I apologize for not having a score sheet in front of me for this question.

Let's take Question 10A. How confident are you that these conclusions are generalizable? No matter what your findings were, no matter what your conclusions were. How confident are you that those conclusions are generalizable to the Medicare patient population?

If you're not confident about the generalizability, that's closer to the bottom of the scales. If you are confident, closer to the top of the scale.

And I see a 3.875. Thank you very much. Dr. Phurrough.

DR. PHURROUGH: Steve Phurrough, five.

MS. CABRAL-DANIELS: Rene Cabral-Daniels, four.

MS. ELLIS: Peter Heseltine, four.

DR. JANOWITZ: Warren Janowitz,

four.

DR. MCDONOUGH: Rob McDonough, four.

DR. SAADI: Ryan Saadi, four.

MR. SAMSON: David Samson, three.

DR. STEINBROOK: Robert Steinbrook, three.

DR. SEAL: Brian Seal, four.

MS. ELLIS: Dr. Rudy, three.

DR. GOODMAN: Okay. Thank you all very much. Excellent.

Now let's ask the same question, 10B, for community-based settings. The rational behind this is that sometimes evidence is generated in settings that are ideal, or highly protocolized, or well-controlled, or well-managed, unusual and so forth.

And we care about how things, Medicare programs cares about how well things work in the real world. i.e., community-based settings or real world settings. Dr.

McDonough, question.

DR. MCDONOUGH: Maybe an obvious one, community settings in the United States?

DR. GOODMAN: Yes, sir. One well made. Okay, let's vote on that. Highly confident, five. Not confident at all, one. Intermediate confidence would be a three. I see a 3.625. Dr. Phurrough, your vote.

DR. PHURROUGH: Five.

MS. CABRAL-DANIELS: Rene Cabral-Daniels, four.

MS. ELLIS: Peter Heseltine, four.

DR. JANOWITZ: Warren Janowitz, four.

DR. MCDONOUGH: Bob McDonough, three.

DR. SAADI: Ryan Saadi, three.

MR. SAMSON: David Samson, three.

DR. STEINBROOK: Robert Steinbrook, three.

DR. SEAL: Brain Seal, four.

MS. ELLIS: Dr. Rudy, three.

DR. GOODMAN: Great. Thank you very much. Okay. We're going to have a few closing comments, but, Ms. Ellis, if I'm not mistaken, we've covered all of our questions.

MS. ELLIS: That's correct.

DR. GOODMAN: Voting and non voting. All right then.

Does anyone who was a speaker today, before we go to panel, does any speaker have a final, well-phrased, concise comment, that they want to make before we adjourn for the day. Actually go back to our panel for final comments.

Anything that should be on the table, that's not. Any major important thing that we missed, that you haven't all ready cited? Okay. Seeing none.

Final comments and, I'll -- we'll do a forcing function here. Dr. Seal, we're going to start with you and just go right down the row here. If you've already said something that you want to lay with us, don't

need to repeat it, that's fine. But any final closing comments. What's your last word, Dr. Seal?

DR. SEAL: The technology seems like it is very useful. In my opinion some additional studies are required to see where we could fit it into sighting and into the use with the medical practice.

DR. GOODMAN: Thank you. Dr. Steinbrook.

DR. STEINBROOK: Well, just talk about it, the improvements on the standard 12-lead EKG would be welcome. And I think despite some of the overall conclusions here today, in terms of where the evidence is now, that there are ample opportunities and I encourage people are working on this to keep going.

DR. GOODMAN: Yes. Thank you, Dr. Steinbrook. Next will be Mr. Samson. Mr. Samson.

MR. SAMSON: Nothing to add.

DR. GOODMAN: Thank you. Dr. Saadi.

DR. SAADI: Just one quick thing is that for industry this is important to recognize one priority. That the evidence, the definition of evidence they could be different. Between CMS and FDA.

DR. GOODMAN: Thank you. Dr. Saadi, Dr. McDonough.

DR. MCDONOUGH: I guess on that point, I mean the evidence standards might be a little bit different with private peers and CMS, I mean, obviously we're dealing with a somewhat different population.

DR. GOODMAN: Thank you, Dr. McDonough. Dr. Janowitz. Any final comments, sir.

DR. JANOWITZ: No.

DR. GOODMAN: None by Dr. Janowitz. Ms. Cabral-Daniels.

MS. CABRAL-DANIELS: I would like to direct my final comments to the Agency, and

that would be to encourage the paradigm shift in terms of looking at different stake holders, and when looking at the questions.

DR. GOODMAN: Great. Thank you. Dr. Phurrough.

DR. PHURROUGH: I think there are some significant potentials here in this technology. I think MCG appears to be moving in a positive direction for data collection. Unfortunately we didn't have a lot of that data to review, since one of the main ones is a recent study.

I think that's encouraging, and hopefully as these other technologies. Hopefully these other technologies will also take the time to develop the evidence base that makes patients and payers and clinicians more comfortable with the technology.

DR. GOODMAN: Great. Thanks Dr. Phurrough. Before I turn it back over to Dr. Rollins. A few other closing comments.

First, today we saw, we've seen

available evidence, as best we could. In this instance there were few studies. Most of them were not very strong. Or I should say in general, the body of evidence was not very strong.

We did look for the best evidence, and that is an important phrase, best evidence where we could find it. It wasn't the best of evidence. But we did make some specific findings. I would reiterate that MEDCAC can only appraise the evidence that's brought to it.

And whether that's a matter of timing. That's one issue, whether it's a matter of not being in the peer reviewed literature. Whether it's a matter of being, not being in inclusion criteria for a technology assessment or systematic review. We can only deal with the evidence brought before us.

And so just a point to be made to innovators, industry and so forth, is that to

the extent you can anticipate the kind of evidence that policy makers may need. Or other decision makers may need. Or evidence appraisers may need. You want to be ahead of the curve, not behind it. We can only appraise what's in front of us.

Next, there is a difference. There are many differences between FDA expectations, or any regulatory agencies expectations. And the needs of coverage decision makers. And as Dr. McDonough pointed out, there are different needs among Medicare, state Medicaid, commercial insurers, and so forth.

And honestly from the stand point of innovators, they've got to deal with multiple regulators around the world, and multiple payers. So it's not and easy road to hoe there. But there are distinct differences.

Next, when you deal with screening tests, diagnostic tests, it's just not enough

anymore to show that you've got a sense of this specific test performance. Characteristics are necessary. But they are no longer sufficient.

While it is sometimes difficult, but not always, to draw lines from a test to a finding that's reliable. A finding to a decision, and a decision to help outcome. That's what we're seeking more and more.

It's not just the Medicare program, I can assure you. It's health authorities around the world, in the public and the private sector. This is not just something that Medicare does. In fact in some ways Medicare's trailing a little bit on the insistence for that kind of, for that kind of evidence.

And by the way, the more you come to meetings like this or watch their results, or similar kinds of meetings that appraise evidence. You're going to see the same thing over and over.

More and more, decision makers, and I don't mean just peers. Patients, clinicians, and others are saying more and more, we want, real world evidence. Not just eye evidence from idealized settings. We want to have comparators. Real comparators, real world comparators.

And we care about health care outcomes. And more and more within health care outcomes, we care about patients centered or patient oriented outcomes.

This is a consistent message you're going to hear over and over. If you think you heard it today, I wish it wasn't the first time you heard it. But I can promise you also, it won't be the last time you're going to hear it.

So I think this is was a very helpful day today for our panelist. Thank you all very, very much for your effort. All the way up and down the line. Thank you very much for the attention, the homework you had to do

leading up to this. Thank you very much for our guest speakers, all of you.

Especially those of you that stayed for the entire day. And were most attentive and were highly, and specifically, and insightfully responsive, to our quite diverse questions.

I know it takes lot to go through a day like this. I know your day started very, very early. We very, very much appreciate on behalf of MEDCAC and the agency. Your presence and willingness to take part in this.

We are further very much appreciative of the technology assessment team, for Evidence Based Practice Center. In particular Dr. Coeytaux and Mr. Leisy, for standing and sitting so very frequently and coming up with these excellent responses.

Thank you very much as well to Lisa Eggleston for her initial presentation for voting questions and so forth. Thank you, Dr. Miller, Dr. Rollins, Ms. Ellis, for making

sure that everything runs smoothly on time. People come and go as they need to. With that I'll turn it over to Dr. Rollins.

DR. ROLLINS: Let me just say that I would like to echo everything that the panel members have said. And as I said earlier today, MEDCACs basically serve a number of purposes. Number one, we can get information from experts in the field. And number two, be able to disseminate this information to the general public.

I'd like to thank the members of the MEDCAC committee. Especially the chairperson, the vice-chair person, as well as the speakers and everybody else in the audience for participating in this afternoon and this mornings discussion. Thank you. Thank you all.

DR. GOODMAN: I guess we are adjourned.

(Whereupon, the above-entitled matter went off the record at 3:10 p.m.)

C

G

U

C E R T I F I C A T E

This is to certify that the foregoing transcript

In the matter of: Medicare Evidence Development and Coverage Advisory Committee

Before: CMS

Date: 11-09-11

Place: Baltimore, MD

was duly recorded and accurately transcribed under my direction; further, that said transcript is a true and accurate record of the proceedings.

Neal R. Gross

Court Reporter