

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

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MEDICARE EVIDENCE DEVELOPMENT & COVERAGE  
ADVISORY COMMITTEE

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MEETING

+ + + + +

WEDNESDAY  
NOVEMBER 9, 2011

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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  
RENp 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

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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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1       today's voting questions.

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

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

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

1       you do that.

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

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

18                      Dr. Phurrough.

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

22                      MS. CABRAL-DANIELS: Rene Cabral-

1       Daniels, I likewise, have no conflict of  
2       interest.

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

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

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

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

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

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

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

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

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

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

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

8               MS. ELLIS: Yes.

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

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

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

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

9 Furthermore, for the purposes of  
10 this meeting, SAECG technologies are defined  
11 as those that, assess electrical activity of  
12 the heart and transform and/or interpret the  
13 signal through spatial imaging or advanced  
14 mathematical modeling to produce new indices  
15 and are commercially available in the United  
16 States. This does not include the standard  
17 12-lead ECG or other technologies used only to  
18 diagnose arrhythmias.

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

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

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

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

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

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

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

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

10 Number 5: How confident are you  
11 that there is adequate evidence to determine  
12 whether or not the incremental information  
13 obtained from SAEKG technologies, beyond that  
14 provided by the standard 12-lead EKG, can  
15 eliminate the need at the level of an  
16 individual patient, for diagnostic laboratory  
17 testing, for example troponin, non-invasive  
18 tests of cardiac anatomy or functioning, for  
19 example stress testing or echocardiography, et  
20 cetera or invasive testing of cardiac anatomy,  
21 functioning, for example coronary angiography?

22 Number 6: If the result of

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

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

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

1 health outcomes?

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

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

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

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

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

1 to draw any findings.

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

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

1                   And the final question, Question  
2           10, is about generalizability or external  
3           validity. And this is always a question that  
4           the MEDCAC addresses. And they deal with  
5           whether or not the findings to that point are  
6           applicable in community settings and are  
7           applicable to Medicare beneficiaries.

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

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

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

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

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

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

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

3 (Off microphone discussion.)

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

6 COURT REPORTER: That's fine.

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

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

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

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

1 notes during your talk if we need to ask  
2 questions.

3 DR. MACLEOD: That's fine too  
4 absolutely.

5 DR. GOODMAN: Go ahead.

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

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

22 I want to tell this story really

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

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

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

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

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

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

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

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

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

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

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

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

22 It doesn't always work quite this

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

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

18 And we know, however, that the  
19 error rates are extraordinarily high.  
20 Depending on the literature you look at 30 to  
21 50 percent is the error rate, in both  
22 directions, of misdiagnosing patients with

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

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

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

22             So that's really about the

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

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

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

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

22 And that's what body surface

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

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

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

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

5 And what you see here is, first of  
6 all, fairly low numbers overall.

7 Sensitivities don't get much higher than the  
8 low 80s. Specificity is a little bit, in one  
9 case, a little higher than the mid-80s. So  
10 those numbers are, again, in line with what I  
11 showed you before.

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

1 procedures on patients.

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

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

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

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

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

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

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

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

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

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

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

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

1 most diagnostic ability.

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

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

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

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

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

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

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

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

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

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

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

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

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

4 The torso geometry is something  
5 that's relatively easily available to us today  
6 in the age of modern imaging technologies. CT  
7 imaging, MRI imaging of the whole torso can  
8 provide additional information about the  
9 location of the heart. The location of other  
10 organs within the torso. And that  
11 information, again, helps improve the  
12 diagnostic power of that raw data that's  
13 coming from the body surface.

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

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

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

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

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

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

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

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

1 So you've got an ECG that is a time signal.

2 That's one of the sources that's possible.

3 Another source that we use a lot  
4 is the capturing of the voltage on the  
5 surface, the outer surface, of the heart.

6 That's what this is meant to indicate here.

7 So what are called the epicardial potentials,  
8 or pericardial potentials. The potentials on  
9 the outer surface of the heart.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22 The solution is not unique.

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

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

1 by ischemia. Those changes result in  
2 electrical differences.

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

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

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

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

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

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

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

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

22 So how we do this? What are the

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

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

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

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

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

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

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

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

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

1       so many years to even get useful solutions.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1       That's one approach to doing it.

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

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

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

10 DR. GOODMAN: Five minutes. Thank  
11 you.

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

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

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

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

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

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

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

1 cannulation system and generate localized  
2 ischemia.

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

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

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

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

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

1 to say something about this.

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

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

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

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

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

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

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

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

22 Do any of these devices actually

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

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

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

22                   So there's a lot of similarity in

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

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

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

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

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

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

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

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

14 DR. MACLEOD: Great.

15 DR. GOODMAN: Thank you very much.

16 DR. MACLEOD: Thank you.

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

22 Welcome, Dr. Fleg. And I'll just

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

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

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

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

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

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

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

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

22 But the major presentations are

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

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

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

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

15 And unfortunately many of these  
16 patients do not even make it to the hospital  
17 to be treated. The incidence of acute  
18 myocardial infarction about a million cases  
19 annually in the U.S. and sudden cardiac death  
20 200,000 to 400,000. So these are both highly  
21 prevalent conditions. The number of patients  
22 living with coronary artery disease in the

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

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

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

22 So the more of these risk factors

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

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

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

1 relieving factors.

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

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

1 exercise is mainly increased demand.

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

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

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

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

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

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

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

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

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

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

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

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

22           Retinal arteriolar changes,

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 the actual severity of disease if you do  
2 intravascular ultrasound.

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

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

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

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

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

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

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

22 So first we'll talk about the

1 standard treadmill exercise test, which can  
2 also be done of course on a cycle odometer.  
3 We used graded exercise through exhaustion.  
4 A positive test is defined as a flat or down  
5 sloping ST-segment depression of at least one  
6 millimeter. And the sensitivity of this  
7 finding for coronary disease is about 65  
8 percent at, you know, the numbers I'm going to  
9 give you are general averages from multitudes  
10 of studies. Specificity is around 70  
11 percent. But if someone has an abnormal  
12 resting electrocardiogram the specificity can  
13 be much lower. And, in fact, if somebody  
14 really has a grossly abnormal resting  
15 electrocardiogram with ST-segment changes at  
16 rest, then we would probably go to an imaging  
17 test right off the bat, because the  
18 specificity is just so poor that it's not  
19 going to tell you much.

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

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

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

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

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

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

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

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

1 always preferable to a pharmacologic stress  
2 test. Sensitivity of stress echo, actually  
3 that number should be about 80 to 90 for  
4 sensitivity. And the specificity about 85 to  
5 90 percent. It's certainly more sensitive,  
6 and also more specific than the stress EKG,  
7 because we're actually imaging the test. A  
8 positive test is a new regional wall motion or  
9 abnormality in the left ventricle that was not  
10 present at rest, evidence of inducible  
11 ischemia in the left ventricle.

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

1 DR. GOODMAN: About two minutes.

2 DR. FLEG: Two minutes? How much?

3 DR. GOODMAN: About two minutes.

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

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

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

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

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

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

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

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

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

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

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

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

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

7 DR. FLEG: Well, balance of the  
8 morning.

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

11 DR. FLEG: Yes.

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

14 DR. HESELTINE: I have.

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

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

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

1 identifying ischemia is in the symptomatic  
2 patient.

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

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

19 And so on acute myocardial  
20 infarction, to diagnose infarction requires a  
21 rise and fall of the biomarkers, either  
22 troponin or CKMB as the two standards of

1 myocardial necrosis.

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

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

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

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

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

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

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

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

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

1 Analysis Technologies for Evaluating Acute  
2 Coronary Syndrome.

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

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

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

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

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

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

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

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

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

22 The resting 12-lead

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 negative.

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

6 These inherent limitations of the  
7 resting 12-lead EKG has inspired the  
8 development of novel approaches for the  
9 detection of cardiac ischemia or infarct.

10 Among these is what we're referring to as  
11 ECG-based signal analysis devices, or SAEKG.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

16 2c is what is the evidence that  
17 ECG-based signal analysis technologies impact  
18 diagnostic decision-making?

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

22 This slide illustrates our

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

20                  (No response)

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

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

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

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

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

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

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

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

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

19          So there are 3 papers that  
20          duplicate studies but had new information, so  
21          11 studies and 14 publications.

22          Key question 2a, this had to do

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

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

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

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

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

22 Key question 2b is really where

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

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

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

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

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

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

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

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

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

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

1                   And the LP 3000, the sensitivity  
2                   was 69 percent compared to 56 percent for the  
3                   ECG and those differences were not  
4                   statistically significant for this study, and  
5                   the specificity was the same for both tests at  
6                   89 percent.

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

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

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

1 evolving over time.

2 We conducted a meta-analysis of  
3 eight of the ten studies of the PRIME ECG.  
4 The results of this meta-analysis suggest that  
5 the sensitivity for the PRIME ECG for  
6 diagnosing acute MI is 68 percent compared to  
7 41 percent for the 12-lead ECG.

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

12 Our estimates for the specificity  
13 for the PRIME ECG is 91 percent, compared to  
14 95 percent for the 12-lead ECG. And positive  
15 and negative likelihood ratios were not  
16 significantly different between these two  
17 devices.

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

22 And for key question 2d, we

1 identified two studies that provided pertinent  
2 information. The large OCCULT trial enrolled  
3 1,830 patients including patients with STEMI.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22              They have a device that's been

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

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

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

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

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

1 biggest limitations of the existing  
2 literature.

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

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

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

21 Other subgroups that might be  
22 relevant for study include conditions that

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

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

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

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

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

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

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

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

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

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

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

1 DR. COEYTAUX: Very good, thank  
2 you.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

14 DR. GOODMAN: We hope so. Keep  
15 talking.

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

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

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

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

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

22                  And we made the judgment call that

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

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

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

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

21 DR. PHURROUGH: Yes, thank you.

22 DR. GOODMAN: Thank you. And the

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

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

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

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

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

1 McDonough was first, I believe.

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

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

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

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

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

22 And the reason I'm asking that

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

5 DR. COEYTAUX: Yes.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

20 DR. COEYTAUX: That is correct.

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

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

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

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

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

11                   DR. GOODMAN: Mr. Leisy.

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

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

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

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

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

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

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

16 (No response)

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

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

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

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

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

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

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

1       that that is the intended role of the test?

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

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

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

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

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

22                   We did read a number of editorials

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

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

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

9 DR. STEINBROOK: Thank you. I  
10 wanted to draw you out a bit to elaborate on  
11 the issue with the PRIME ECG of the so-called  
12 limited evidence of patients with ST-elevation  
13 detected by the PRIME ECG having increased  
14 mortality as compared to that not being the  
15 case when ST-elevation was determined with the  
16 12-lead ECG.

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

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

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

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

15                  DR. STEINBROOK: Sure.

16                  DR. COEYTAUX: Great, thank you.

17                  DR. GOODMAN: Okay, yes, go ahead.

18                  Dr. Janowitz I think was next.

19                  DR. JANOWITZ: I had the same  
20                  question so.

21                  DR. GOODMAN: Okay. Dr.  
22                  Heseltine.

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

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

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

13 DR. GOODMAN: Closer to the  
14 microphone, please.

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

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

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

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

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

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

15                  DR. HESELTINE: Yes.

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

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

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

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

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

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

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

1 actually question number one.

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

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

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

15 DR. COEYTAUX: Dr. Steinbrook's.

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

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

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

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

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

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

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

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

16 DR. COEYTAUX: Yes, this --

17 DR. GOODMAN: So stop.

18 DR. COEYTAUX: Yes.

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

21 DR. COEYTAUX: Yes, please.

22 DR. GOODMAN: Do proceed.

1 DR. COEYTAUX: Thank you.

2 Two-part question as I understand. The first  
3 part of the question is how confident are we  
4 given the heterogeneity of the studies in  
5 doing a meta-analysis and being confident in  
6 the validity of our findings? Is that the  
7 correct question?

8 DR. SAADI: Yes.

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

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

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

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

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

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

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

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

1 reasonable combining of outcome.

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

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

11 DR. SAADI: Okay.

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

15 DR. COEYTAUX: One moment, please.

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

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

1 was associated with an increased mortality,  
2 odds ratio 11.2, confidence interval 1.8 to  
3 67.

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

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

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

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

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

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

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

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

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

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

20           DR. GOODMAN: Thank you.

21           MR. LEISY: You're welcome.

22           DR. GOODMAN: Dr. Steinbrook, you

1       okay with the response?

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

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

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

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

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

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

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

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

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

22          There is evidence that has

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

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

7               DR. STEINBROOK: Thank you. Thank  
8       you.

9               DR. GOODMAN: Okay.

10              DR. COEYTAUX: Okay, thank you.

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

16              DR. COEYTAUX: Yes.

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

22              DR. JANOWITZ: Is there any data

1 concerning gender differences on this  
2 technique?

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

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

13 DR. GOODMAN: Thank you. Mr.  
14 Samson.

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

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

1 in the evidence base.

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

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

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

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

22 As far as the clinical one, this

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

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

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

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

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

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

1 really don't know so that --

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

4 DR. GOODMAN: Briefly.

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

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

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

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

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

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

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

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

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

22                  DR. GOODMAN: Good, thank you.

1 This is our last question for this segment.

2 Dr. McDonough, did you have a closing for this  
3 section?

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

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

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

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

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

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

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

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

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

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

1 of it.

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

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

11 DR. GOODMAN: Thank you.

12 DR. COEYTAUX: Is that  
13 satisfactory?

14 DR. MCDONOUGH: Yes.

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

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

1       that was not our last opportunity.

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

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

14              MCG is entirely different than  
15      12-lead ECG, a resting or a stress ECG, in  
16      that matter. MCG focus on systems theory  
17      using the, study the communication between  
18      different parts of a system.

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

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

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

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

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

1       caused by the interaction.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1       sure that bias is eliminated.

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

8               And, again, as I said, 50 percent  
9       of the people in the database are women and  
10      that's the reason why perhaps MCG can provide  
11      equal accuracy for men and women in the same  
12      age group. The age range, again, from 14 to  
13      100.

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

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

1 as 30, 40 percent to 100 percent.

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

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

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

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

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

1 effectively with high sensitivity/specificity.  
2 Thank you.

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

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

11 DR. SHEN: I'm sorry?

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

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

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

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

6                   I would like to talk briefly about  
7                   some validation studies including more than  
8                   1,000 patients scheduled for coronary  
9                   angiography done with MCG.

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

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

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

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

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

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

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

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

1 throughout different subgroups.

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

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

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

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

1       these different subgroups.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

3 DR. IMHOFF: Correct.

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

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

8 DR. GOODMAN: Thank you.

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

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

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

1 inclusion criteria.

2 DR. GOODMAN: Right.

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

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

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

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

1       cardiogram. I have no disclosures.

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

8               And I'm going to talk about the  
9       direct comparison data of MCG to SPECT  
10       Myocardial Perfusion Imaging which was  
11       recently published.

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

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

1 coronary artery disease who undergoing  
2 elective catheterization.

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

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

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

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

1       percent had normal exams.

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

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

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

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

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

1       need it.

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

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

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

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

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

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

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

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

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

1 based setting.

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

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

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

13 That sensitivity and specificity  
14 difference persisted for females and when  
15 accuracy was looked at the accuracy of MCG  
16 compared to the accuracy of stress perfusion  
17 imaging was considerable different.

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

22 I want to talk a little bit about

1 the important questions.

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

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

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

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

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

1 DR. STROBECK: Thank you, very  
2 much.

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

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

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

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

1 QRS analysis.

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

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

8 DR. BEKER: Okay. Next slide  
9 please.

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

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

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

1 Main implications of stress test

2 low clinical accuracy include unnecessary  
3 radioactive and invasive follow-up tests.

4 High percentage of false negative cases and  
5 excessive costs to the health system.

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

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

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

22 By the way, the changes in high

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

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

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

16 One of the two examples I have  
17 here for a study demonstrating the clinical  
18 value of High-Frequency QRS technology is this  
19 one.

20 This study was excepted for  
21 publication in the American Journal of  
22 Cardiology after this presentation was

1 submitted to the committee organizer. So the  
2 reference there should be in press, or  
3 accepted.

4 The study included 941 consecutive  
5 patients referred to SPECT cardiac nuclear  
6 imaging for evaluation of coronary artery  
7 disease.

8 All patients underwent stress ECG,  
9 stress HyperQ tests and cardiac nuclear  
10 imaging. Results and conclusions of the study  
11 HyperQ index offered significant improvement  
12 of the diagnostic value over clinic exercise  
13 tests.

14 Linking it to the questions  
15 discussed today, higher diagnostic value  
16 improves physician decision making.  
17 Especially in inconclusive and non-diagnostic  
18 populations. Improves patient outcomes and  
19 reduces the rate of unnecessary radioactive  
20 and invasive procedures.

21 A ST segment analysis high  
22 frequency QRS analysis has shown gender

1 independence sensitivity and specificity and  
2 marked improvement of clinical accuracy in  
3 women.

4               Following is a summary of the  
5 study in women population where the reference  
6 standard used was angiography for all enrolled  
7 patients. Again the results demonstrated  
8 significantly improved clinical accuracy  
9 compared with stress testing.

10              Suggesting that the incorporation  
11 of High-Frequency QRS analysis into the  
12 diagnostic routine may improve the currently  
13 deficient diagnostic outcomes in the women  
14 population. And may reduce the number of  
15 unnecessary angiographic procedures in women.

16              More clinical studies support the  
17 increased sensitivity and specificity of  
18 stress HFQRS, or High-Frequency QRS, performed  
19 as part of and in conjunction with clinical  
20 stress testing procedures.

21              Do to the limited scope and time  
22 of this presentation I did not include here

1 references to the growing number of studies  
2 focusing on the performance of High-Frequency  
3 QRS analysis in non stress conditions. And  
4 demonstrating its increased clinical accuracy  
5 in detecting myocardial ischemia and acute  
6 coronary syndrome.

7 Summarizing the main merits of  
8 High-Frequency QRS and the benefits of its  
9 inclusion in the clinic work up for the  
10 evaluation of ischemic heart disease.

11 Improved sensitivity decreases the  
12 rate of false negative results. Improved  
13 specificity prevents or reduces unnecessary  
14 further radioactive tests.

15 Improved accuracy in women allows  
16 better clinical evaluation of women for  
17 ischemic heart disease and improved standard  
18 of cardiac care for these under served  
19 populations.

20 High-Frequency QRS provides the  
21 clinician, both in major hospitals and the  
22 community with a better tool for an accurate

1 first line diagnoses of ischemic heart  
2 disease.

3 The technology is very effective  
4 in elderly patient populations and currently  
5 inconclusive in non diagnostic patients.

6 Please allow me to conclude.  
7 Improvements to first line cardiac diagnostic  
8 tests has significant impact on health  
9 outcomes, High Frequency QRS analysis during  
10 stress testing has demonstrated significantly  
11 improved clinical accuracy for the detection  
12 and diagnostics of ischemic heart disease.

13 HFQRS is currently being evaluated  
14 in the real life testing under a registry  
15 study in several U.S. sites. And this may be  
16 an excellent opportunity to provide coverage  
17 and capture data at the same time

18 We believe that devices that  
19 incorporate HFQRS analysis in stress ECG  
20 testing and that are cleared by FDA should be  
21 incorporated in coverage policies of the CMS.

22 Thank you very much.

1 DR. GOODMAN: Thank you very much,  
2 Dr. Beker. If you could just stay there for  
3 just a moment, I want make sure that I  
4 understand something.

5 The device of which you spoke is I  
6 believe, listed in the technology assessment,  
7 it's listed as HyperQ stress ECG from  
8 biological signal processing. That's the same  
9 device?

10 DR. BEKER: That's correct.

11 DR. GOODMAN: And this was a  
12 technology for which the technology assessment  
13 team found no in scope studies. It wasn't one  
14 of the 11.

15 DR. BEKER: Not one of the 11,  
16 yes.

17 DR. GOODMAN: Was not one of the  
18 11.

19 DR. BEKER: It was one study which  
20 was not included in the 11 and the study that  
21 was just presented here was not yet published  
22 or accepted for publication, so they could not

1 see it.

2 DR. GOODMAN: Exactly, it went by  
3 pretty quickly but I noticed that at least two  
4 of the citations that you provided were indeed  
5 abstracts not full articles published.

6 DR. BEKER: One was accepted and  
7 other is in preparation as are some other  
8 studies, in preparation for publication.

9 DR. GOODMAN: Okay. Good, I just  
10 wanted to make sure I understood that we had  
11 identified the appropriate device and  
12 understood the publication status.

13 DR. BEKER: You have, yes.

14 DR. GOODMAN: Thank you very much,  
15 Dr. Beker. We appreciate your time. Thank  
16 you, sir.

17 Okay, panel we're still in pretty  
18 good shape on time and I'll just confirm with  
19 Maria Ellis one more time. I believe we did  
20 not have submitted same day comments, is that  
21 correct?

22 MS. ELLIS: That's correct.

1 DR. GOODMAN: Okay. So we've  
2 picked up a little bit of time there we're  
3 actually not too far behind. The portion of  
4 our agenda at this point, concerns questions  
5 to presenters.

6 We've already gone down that road  
7 a bit so I think we're in good shape. If I  
8 could I would like to ask those that have  
9 presented this morning to make their way to  
10 the front row of the room in case. It's  
11 easier for us easier to pick on you. Find  
12 you.

13 And especially the two TA guys  
14 pretty close to front and center, and our four  
15 presenters, I don't know that Dr. Fleg is  
16 still here he's got to leave, there he is. I  
17 know he has to leave in a little bit, and Dr.  
18 MacLeod as well. So we can now find you, this  
19 is great.

20 Okay, panel, just reminding all of  
21 us that while we may have questions a plenty  
22 for the material presented thus far today. We

1 really do want to focus on the questions that  
2 we're going to have to answer before we're  
3 allowed to leave this exalted hall.

4 So when you do think of your  
5 questions it would help a lot to make sure  
6 that you're kind of pinning them to one of our  
7 questions. And that we'll try to keep the  
8 discussion focused that way. And I saw Dr.  
9 Phurrough's hand shoot up right away. Dr.  
10 Phurrough.

11 DR. PHURROUGH: Thank you. Dr.  
12 Imhoff.

13 DR. GOODMAN: We have to all speak  
14 directly into our mics I am told.

15 DR. PHURROUGH: Yes. You listed,  
16 on your second slide, three study centers are  
17 those studies listed in the reference to the  
18 TA as being excluded?

19 DR. IMHOFF: Correct. That's my  
20 understanding.

21 DR. PHURROUGH: Which are those?  
22 Could you just point that out to me so at

1       some, perhaps at lunch time you can show me  
2       what those studies are.

3               DR. GOODMAN: Do you know off hand  
4       the first author of those studies, it would  
5       make it easier to find.

6               DR. IMHOFF: The first author of  
7       the German studies is Grube, and the author of  
8       the Asian Multicenter Trial is Hosokawa and  
9       the author of the Westchester Trial is Weiss.

10              DR. PHURROUGH: Okay, if I could  
11      then skip to one of the two TA people to  
12      answer the question of the exclusion of those  
13      two particular studies.

14              DR. GOODMAN: This is Mr. Leisy  
15      coming to the microphone.

16              MR. LEISY: So we have, there are  
17      actually four publications from those three  
18      cites. Two from the Germany cite from Dr.  
19      Grube. And then one is the Asian Multi  
20      centers studies to Hosokawa, and the last one  
21      is the one from New York which is the Dr.  
22      Weiss et al 2002 study.

1                   Now the differences, that was a  
2                   very good presentation earlier that we saw.  
3                   They indicated that these studies looked at  
4                   only the low to intermediate risk patients  
5                   population.

6                   But the definition for the  
7                   population was based on the results of the  
8                   angiographic findings, not on the patient  
9                   presentation.

10                  And so the criteria that we used  
11                  was based on the updated American Heart  
12                  criteria published in 2010 on the management  
13                  of acute coronary syndrome. Based on the  
14                  presenting patient, most likely the presenting  
15                  12-lead ECG.

16                  And if I can just refresh, it has  
17                  risk stratification from high risk. Two  
18                  categories of high risk and then a low to  
19                  intermediate risk for acute coronary syndrome.

20                  The high risk is the systemic  
21                  population, ST elevation, myocardial  
22                  infarction. Another high risk is the STEMI

1 equivalent or ST depression in the anterior  
2 leads and also acute T-wave inversions.

3 And the last one, the low to  
4 intermediate risk for acute coronary syndrome  
5 is, patients that present with chest pain and  
6 or symptoms suggestive of a coronary event.

7 That have either normal or non  
8 diagnostic changes in the ST or the T-wave.  
9 And that was from the 2010 publication of  
10 American Heart guidelines for manage of acute  
11 coronary syndrome.

12 So I think the difference in the  
13 studies and we really struggled with these  
14 studies as well. Because I know they're  
15 included in the 2010 report.

16 Was that the presentation of the  
17 patients in these four 3DM studies were all  
18 preselected for coronary angiography and their  
19 presentation to the clinics or the outpatient  
20 centers was not given. And so we concluded  
21 that based on all of them being selected for  
22 coronary angiography would have selected

1 patients in a higher risk based on the AHA  
2 guidelines of patient presentation. Does that  
3 answer your questions?

4 DR. GOODMAN: Okay. Thank you  
5 very much. Further questions at this point.  
6 Dr. Steinbrook.

7 DR. STEINBROOK: This is a  
8 question with regard to the technology  
9 assessment. And key question 1A when you had  
10 the list of the devices, point of information  
11 and then a question. The point of information  
12 is several of these devices are listed as not  
13 FDA cleared.

14 But I presume that they are still  
15 commercially available, that makes no  
16 difference in terms of their commercial  
17 availability in terms of the way you asked the  
18 question. Am I correct with that?

19 DR. GOODMAN: You need to speak  
20 into a microphone, Dr. Coeytaux.

21 DR. COEYTAUX: Just very briefly  
22 with that. We look at those two

1 independently, whether they were available in  
2 the U.S. or whether we found evidence of FDA  
3 clearance. We looked at separately. Does  
4 that answer your question?

5 DR. STEINBROOK: No, I'm confused  
6 again. It's more just a point of information  
7 about the FDA process. For the device to be  
8 commercially available in a country does it  
9 have to be FDA cleared? That's the question,  
10 because are all these commercially available,  
11 all of these 11?

12 DR. COEYTAUX: No. There's one  
13 from Slovakia, two of them from Slovakia, the  
14 Procardio for example that are not available  
15 in the United States and they also happen to  
16 not be FDA cleared.

17 DR. GOODMAN: Commercially  
18 available somewhere.

19 DR. COEYTAUX: Somewhere, but not  
20 in the United States. The two can be, you can  
21 have one and not the other for that original  
22 list, I believe.

1 DR. STEINBROOK: Probably not  
2 worth belaboring but the ones in Table 1, are  
3 they all available in this country?

4 DR. COEYTAUX: No.

5 DR. STEINBROOK: Oh, eight of the  
6 11 are, the ones that are -

7 DR. COEYTAUX: Is Procardio in that  
8 Table 11?

9 DR. STEINBROOK: I don't think it  
10 is there at all.

11 DR. COEYTAUX: Okay, that is one  
12 they removed it for. Actually I'm going to  
13 have Mr. Leisy answer the question because he  
14 really focused on Question 1a. Do you want to  
15 come up here and address that.

16 DR. GOODMAN: Mr. Leisy.

17 MR. LEISY: So on the gray  
18 literature search we initially did not exclude  
19 devices that were either commercially  
20 available or that were not commercially  
21 available or were not FDA approved.

22 We tried to cast a giant, huge net

1 so we could catch all devices potentially and  
2 then any device that we found based on the  
3 gray literature research we then cross  
4 referenced that based on either the  
5 manufacturer website or any distribution  
6 website and we attempted to locate a source of  
7 distribution.

8 If we found the source of  
9 distribution then we included it as a relevant  
10 device. Now we did look for commercial  
11 availability in the United States for relevant  
12 device where we had difficulty was finding the  
13 current FDA approved status for a couple of  
14 devices. Are we able to speak on if we found  
15 conclusion on some of those?

16 DR. GOODMAN: The answer to that  
17 question was no, by the other staff person  
18 from the TA. Dr. Steinbrook.

19 DR. STEINBROOK: So to follow to  
20 my more substantive question, did you in the  
21 process of doing your various literature  
22 searches for information. Was there any

1 information available from the FDA as part of  
2 the clearance processes?

3 Or any other FDA activity or  
4 submissions to the FDA related to any of these  
5 devices which was relevant to your attempt to  
6 answer some of the other questions with data?

7 MR. LEISY: The FDA website was  
8 one of the resources we used for the gray  
9 literature search. We had a predetermined  
10 product codes that were a category of devices  
11 that were relevant for our study.

12 I searched those product codes and  
13 we looked at each of the FDA status or  
14 applications for FDA status as well for these  
15 devices and those that were produced.

16 I think we found two or three that  
17 were, one is the Philips I believe, maybe two  
18 Philips devices I'd have to go reference the  
19 table. But we did find a couple of devices  
20 directly from the FDA website.

21 We also looked at clinical trials  
22 to see if there was any devices pending or

1       that might have been pending that were applied  
2       for FDA status as well. Does that answer your  
3       question?

4                   DR. STEINBROOK: Yes, thank you.

5                   DR. GOODMAN: Question, Ms.  
6       Cabral-Daniels.

7                   MS. CABRAL-DANIELS: First I want  
8       to commend the group for all the hard work  
9       that's been done. I do have a question with  
10      regard to Dr. Coeytaux, you had mentioned that  
11      in looking at the data before and looking at  
12      different studies.

13                   I think the question came up with  
14      regard to any data with regard to women and  
15      you said that was something that you looked  
16      at. What other variables did you look at?

17                   Were there any other areas that  
18      you might want to share with the panel that  
19      you found to be interesting although they may  
20      have been somewhat tangentially related?

21                   DR. COEYTAUX: Yes, and I thank  
22      you. I noticed that there were good data for

1 the other studies, the other devices that were  
2 included in the TA report on women.

3 But for the prime ECG my  
4 recollection is that they did not have  
5 subgroup analyses for women. Part of one of  
6 the key questions I believe it was 2b, was to  
7 look at factors that effect the outcome or the  
8 efficacy and they way the data reported there  
9 was just nothing there that we could use,  
10 unfortunately.

11 DR. GOODMAN: And that was Ms.  
12 Cabral-Daniels. I mispronounced your name, I  
13 apologize. It looks like, Dr. Rudy.

14 DR. RUDY: Yes, I have a question  
15 to Dr. Coeytaux also regarding the data from  
16 Ireland, on the prime ECG it's the seems that  
17 the bulk of the data came from Ireland.

18 And then you mentioned something  
19 about maybe this data are not really relevant  
20 or not really applicable to the way the  
21 clinical practice is conducted here in the  
22 United States. Can you expand a little bit

1       about that?

2                   DR. COEYTAUX:   Yes, we don't know.

3       Now in terms of the applicability we felt it  
4       was our responsibility to at least point out  
5       the fact that we had some questions about  
6       that.

7                   The two questions that we had  
8       about Ireland.  One is, two points of comment.  
9       One is that they develop the technology and  
10      were experimenting with it in the field and  
11      they developed in the field and were very good  
12      about documenting it in the publications.

13                  Which we would think is a very  
14      good thing.  But need to be noted because they  
15      were developing as their publications, as they  
16      were writing their publications.  And we  
17      wanted to make a note of that.

18                  What we really did not know,  
19      nobody on our team could really assess is the  
20      impact on the patient population of having  
21      essentially a mobile cardiac unit that goes to  
22      the field and is staffed by cardiologists,

1 intensive care cardiologists.

2 And we just don't know whether or  
3 not that reflects a different patient  
4 population than those in the United States who  
5 tend to be transported to the emergency room  
6 setting. So it's a question we haven't we  
7 didn't know what else to say.

8 DR. RUDY: Okay. Thank you, and  
9 thank you for all the work you've done.

10 DR. GOODMAN: Further questions.  
11 Dr. Saadi, did I see your hand before or was  
12 it Mr. Sampson's hand.

13 MR. SAMSON: Just a question for  
14 the industry speakers. I raised this earlier.  
15 I'm curious about the role of the test in  
16 relation to other tests.

17 Are any of you proposing that your  
18 technology be used as a replacement for  
19 standard ECG or is it generally to be used as  
20 an adjunct or an add on?

21 DR. GOODMAN: This is Dr.  
22 Strobeck.

1 DR. STROBECK: Yes, you know I'm  
2 a practicing cardiologist and have  
3 incorporated the use of the MCG in my clinical  
4 practice over the last two or three years and  
5 have found it to be just invaluable. I think  
6 this technology because of its accuracy --  
7 particularly because of its equal accuracy  
8 between men and women. Can readily help  
9 determine who among a group of eight or ten  
10 people that you're evaluating with symptoms,  
11 suggestive of coronary insufficiency.

12 No change on the EKG or at least  
13 no consistent change -- who have the disease.  
14 So yes, I think it can be used and I think  
15 that the accuracy compared to SPECT nuclear  
16 imaging is significantly better. I think it  
17 could ultimately be used as a determinate for  
18 who needs an invasive strategy of care.

19 MR. SAMSON: So you're saying it  
20 should replace standard ECG or it should be  
21 used as an add on?

22 DR. STROBECK: Not standard ECG

1 no, a standard ECG gives you rhythm based  
2 information. I mean you get some rhythm based  
3 information from the MCG but the MCG's purpose  
4 is to detect coronary obstruction.

5 MR. SAMSON: Okay. So it's an  
6 additional test.

7 DR. STROBECK: It's an additional  
8 test to routine EKG.

9 DR. GOODMAN: Okay. Thank you.  
10 This is Dr. Seal.

11 DR. SEAL: Question on the single  
12 study that you presented, I saw differences in  
13 percentages but I didn't see any differences  
14 in statistical analysis so we didn't see any  
15 confidence intervals, or anything like that.

16 DR. STROBECK: The confidence  
17 intervals have been calculated but they don't  
18 overlap significantly between MCG and SPECT.  
19 Is that what you were saying?

20 DR. SEAL: Right they weren't  
21 presented in your slides, all I seen in the  
22 slides was differences in percentages.

1 DR. STROBECK: Well, the  
2 statistical analysis is in the paper. the  
3 paper is just recently published I think a  
4 copy of it is included in your packet.

5 But the data was statistical  
6 significant at a very high level. When you  
7 compared specificity for example between SPECT  
8 nuclear and MCG was considerably improved with  
9 MCG.

10 DR. GOODMAN: Based on which  
11 study?

12 DR. SEAL: On the single center  
13 study, the paired comparison of MCG with SPECT  
14 myocardial perfusion imaging. 116 consecutive  
15 patients. These are not emergency room  
16 patients, these are patients who are referred  
17 for consultative evaluation.

18 DR. GOODMAN: But, Dr. Seal, if  
19 I'm not mistaken there was no study that made  
20 it through the technology assessment search on  
21 this technology.

22 DR. SEAL: I didn't see it in our

1 packet.

2 DR. STROBECK: Honestly I don't  
3 understand quite how that happened these are  
4 all intermediate risk patients. They  
5 perfectly fit the criteria.

6 Most of them have no resting EKG  
7 abnormalities that are suggestive of  
8 myocardial ischemia. Nothing to put them in  
9 a high risk category. In fact the prevalence  
10 of disease when we did the angiography was  
11 only 43 percent. So I don't know how these  
12 people get classified as high risk.

13 DR. GOODMAN: Okay. Dr. Seal,  
14 just to make sure that we pursue your  
15 question, you can have a seat Dr. Strobeck,  
16 thank you very much. Do either of our people  
17 from our Technology Assessment want to comment  
18 on why the MCG study did not make it all the  
19 way through your process?

20 You started to address this a bit  
21 before, I think when Dr. Imhoff was at the  
22 podium, but if you could just clarify that for

1 us.

2 DR. COEYTAUX: This is Dr.  
3 Coeytaux, is it possible, is there a copy of  
4 the paper here that I can read now just to  
5 comment intelligently on it?

6 DR. GOODMAN: That's not a bad  
7 question. It's not a bad request, sir. If  
8 the folks from Dr. Imhoff or maybe Dr.  
9 Strobeck have that study or can find it for  
10 us. If not this moment, maybe over lunch.  
11 Someone can gin it up for you, I think it's a  
12 fair question.

13 And Dr. Seal, it's an important  
14 question to ask and I think we'll be able to  
15 return to it.

16 Dr. Saadi, I think you were in the  
17 queue, sir, is that correct?

18 DR. SAADI: Yes, I think you  
19 answered my question, just we actually asked  
20 of Dr. Goodman is that of course this  
21 technology will provide benefit in one or the  
22 other in different populations.

1                   But we have to keep the study  
2                   population in mind. If I keep that in mind,  
3                   the Medicare population the U.S. patient  
4                   populations, so I was actually going to ask  
5                   you doctor is. As a practicing cardiologist,  
6                   how do actually see the utility of it? Do you  
7                   actually have clarified that. That you see  
8                   this as an add on, right?

9                   And then moving on to the other  
10                  test procedures. But as a practicing  
11                  cardiologist are you actually willing to put  
12                  a patient, okay so I actually see this and  
13                  it's actually negative. I'm not going to go  
14                  any farther, are you that confident based on  
15                  the data actually you have shown?

16                 DR. STROBECK: Well we did  
17                 analysis, remember these were paired tests.  
18                 So every patient that was in this trial had  
19                 both tests. So we re-analyzed the data using  
20                 the MCG as the determinate for referral for  
21                 coronary angiography.

22                 And when we did that there were

1 five patients that had low MCG scores that  
2 would not have gone for coronary angiography.  
3 But there were 55 patients who had low MCG  
4 scores who were ultimately found on coronary  
5 angiography not to have coronary disease.

6 So there's always a little bit.  
7 It's not perfect but there is a very, very low  
8 incidence of false negatives. And yes, the  
9 answer is yes, I would be very comfortable  
10 with sending a patient. In other words not  
11 referring a patient for catheterization based  
12 on a low MCG score.

13 DR. SAADI: One question.

14 DR. GOODMAN: Go right ahead, Dr.  
15 Saadi.

16 DR. SAADI: So one last quick  
17 follow up question. Would you actually say  
18 that based on the data we have. I mean we're  
19 talking about a very severe consequence,  
20 right? Do you actually feel that we have  
21 enough data as of today, based on actually  
22 what we have seen this morning to actually

1       conclude that kind decision.  If we miss, I  
2       mean I understand --

3                   DR. STROBECK:  Basically for  
4       evidentiary standards we probably don't have  
5       enough data yet.  We're in the process of  
6       doing a randomized control trial where we  
7       compare the MCG score, not just to the  
8       anatomic diagnosis of coronary disease.

9                   But to the functional severity  
10      based on fractional flow reserve.  And we  
11      think that actually is going to improve our  
12      specificity and sensitivity.

13                  DR. GOODMAN:  Good, thank you very  
14      much.  Thank you, Dr. Strobeck.  I'll just  
15      remind everyone in the panel that while we are  
16      interested in our expert speakers views we  
17      necessarily we return to the body of evidence.

18                  And so it's good to hear what Dr.  
19      Strobeck might do in practice as an individual  
20      practicing physician.  That's swell, but we're  
21      more interested in the overall body of  
22      evidence.

1 I think that Dr. Beker wanted to  
2 make a comment before. Is it still relevant,  
3 Dr. Beker? Why don't you approach the  
4 microphone, restate the question that you are  
5 about to answer.

6 MR. SAMSON: Is your technology  
7 intended to be used as a replacement for  
8 standard ECG or as an add on?

9 DR. BEKER: Right and I just wanted  
10 to answer because I think it is a very  
11 important question. Some of the technologies,  
12 including High-Frequency QRS, this question is  
13 not relevant, it's part of the ECG or stress  
14 ECG test.

15 So this is the huge advantage that  
16 for some of technologies. For example a High-  
17 Frequency QRS is preformed exactly at the same  
18 procedure, same electrodes and same placement  
19 of electrodes as the conventional stress ECG  
20 or resting ECG.

21 And it just yields double, or  
22 additional set of results together with the

1 conventional clinical and FDA cleared ECG. So  
2 it's just like having a super ECG for the same  
3 practice or the same procedure of the  
4 conventional one.

5 DR. GOODMAN: Thank you, Dr.  
6 Beker. Dr. Fleg, you want to approach the  
7 microphone, but I hope you have a specific  
8 question that you are about to answer.

9 DR. FLEG: Yes, I do.

10 DR. GOODMAN: Please proceed.

11 DR. FLEG: Well, it's kind of a  
12 challenge to the panel actually that when  
13 you're talking about the diagnostic value of  
14 say the MCG or any of these single averaging  
15 tests in terms of detecting coronary disease.

16 I think that one problem is that  
17 none of these tests, at least as I could see  
18 from the presentations actually localize where  
19 the ischemia is or quantify how much ischemia  
20 is there.

21 When were looking at a patient  
22 with coronary disease it's not really

1 sufficient to say do you have it or do you not  
2 have it? We want to know, is this a high risk  
3 patient that has a large amount of ischemic  
4 myocardia.

5 Because that's the population that  
6 has a much worse prognosis and in whom we  
7 would be more aggressive in terms of doing an  
8 intervention.

9 Simply to detect somebody that's  
10 got, you know, a single vessel with maybe 50  
11 or 60 percent stenosis is not nearly as  
12 important as detecting the high risk patients.

13 So I think you need to keep this  
14 in mind when you are evaluating any of these  
15 single averaging technologies. It's probably  
16 not sufficient in this day and age.

17 It's a nice screening test to say,  
18 you know, they probably have disease. But we  
19 would like to go farther than that. So I  
20 don't think that you can, the issue is I don't  
21 think these can replace imaging until these  
22 test show that they can actually quantify and

1       locate the ischemia.

2                   DR. GOODMAN:   Okay.   Thank you,  
3       Dr. Fleg.   And I'll just remind the panel that  
4       while Dr. Fleg's point is well taken, our  
5       questions B, all the B's deal with patients of  
6       low to intermediate risk, at least a priority.

7                   Okay.   Thank you.   Further  
8       questions at this point for our panelists.  
9       Before we proceed to Dr. Rudy, it appears that  
10      the TA team may have a response to an earlier  
11      question.   Is that correct?   Sure, would one  
12      of you gentlemen approach the mic please?

13                   This concern I believe the MCG  
14      technology?

15                   DR. COEYTAUX:   Yes, it does.   And  
16      thank you, Dr. Shen, for this report.   This is  
17      a study that was just recently published, and  
18      was published after the end of our search.

19                   So it appears to be one that would  
20      be eligible and we will be, it won't help you  
21      today.   But we will be doing a revision and an  
22      updated search for the final draft.   And if at

1       glance we are correct that it's eligible we  
2       will be including this in the report.

3               The reason that this study here,  
4       which is a paired comparison of the MCG, with  
5       the system to be a myocardial perfusion  
6       imaging as a comparator, was not included in  
7       the TA report because it was published after  
8       the window that we had to work with.

9               DR. GOODMAN:   Okay.   Thank you for  
10      the direct answer and thank you for on the  
11      spot investigative reporting.   We appreciate  
12      that very much.

13              And we'll note that typically we  
14      are confined to looking at the literature  
15      that's A, been published and B, that appears  
16      in the Technology Assessment.

17              But that does not mean that in our  
18      considerations that we would necessarily  
19      exclude something just because it did not get  
20      into a Technology Assessment.

21              That doesn't mean, however at the  
22      same time.   That the evidence that may have

1       been discussed is necessarily rigorous or not.  
2       We have to make a judgment about that  
3       ourselves, okay? Just to clarify.

4               Thank you gentlemen for that very  
5       timely help. Dr. Rudy?

6               DR. RUDY: Yes, I have a question,  
7       Dr. Shen, and I need some clarification on the  
8       technology of MCG. If I understand it  
9       correctly MCG's also an analysis approach to  
10      the ECG. So you take an ECG and it's just  
11      like HyperQ is, except you're looking for  
12      something different.

13              So the question is when I look at  
14      your presentation you devise a certain  
15      mathematical approach, the LaGrange  
16      coordinate, to look at visco-elastic  
17      properties of the wall, of the myocardium.  
18      And then you use Euler Coordinates to describe  
19      the non-Newtonian flow of blood.

20              But the ECG measures electrical  
21      activity on the heart, it doesn't look at  
22      motion or profusion. And what's missing in my

1 mind is how do you go from stress and strain  
2 to changes in the electro cardiac activity?  
3 And that's even at the single cell level a  
4 very complicated story.

5 DR. SHEN: Correct, it is very  
6 complicated. First of all, I think the  
7 conceptual approach of this is different  
8 because the Einthoven Model is looking at  
9 single dipole.

10 The dipole is emitting three  
11 dimensionally, you can measure other, use  
12 matching technology or use single 12-lead ECG  
13 to detect one lead at a time, and segments of  
14 the one cardiac cycle, which is fine, it's a  
15 completely acceptable way.

16 DR. RUDY: I understand, but the  
17 measurement is an ECG.

18 DR. SHEN: Well, we're talking  
19 about is that the systems approach, the  
20 LaGrange point of view. Actually it was the  
21 inspiration for us to look at it.

22 The entire approach, say what is

1 the best way to extract more information out  
2 of these ECG signals? Rather than looking at  
3 the traditional way we stepped back and looked  
4 at the LaGrange approach.

5 The instruction to us immediately  
6 was that you need to look at the information  
7 between the two signal sources. That's the  
8 one screaming headline to us. Was that you  
9 cannot look at a single lead at a time. You  
10 have look at both leads.

11 Then what happens is the  
12 information actually traversing, communication  
13 between these two parts as systems approach  
14 The principle thing, the first thing is to  
15 dissect the system into different parts and  
16 see how they communicate with each other.

17 So we're looking at actually for  
18 instance cross power spectrum. Cross power  
19 spectrum actually is looking at the power  
20 distribution at a frequency of a lead two  
21 frequency with V5 power distribution.

22 Now furthermore, look at the

1 histogram, it is the impulse response.

2 Impulse response is actually looking at the  
3 relationship between how the V5 signal is  
4 received or reflected by the Lead 2 signal  
5 source.

6 And so you can actually by using  
7 this mathematical relationship, you can  
8 actually understand how the compliance of the  
9 response of different signal sources give you  
10 extra information.

11 That is why we decided to proceed  
12 with multiple mathematical functions. Each  
13 one of them will give you the information that  
14 is unique rather than the -- I'll be happy to  
15 go over the math with you, one by one, all  
16 functions.

17 DR. RUDY: I didn't want it to go  
18 so long. Just to clarify.

19 DR. GOODMAN: Gentlemen, we have  
20 to speak one at a time please. Dr. Rudy,  
21 proceed.

22 DR. RUDY: Just to clarify, all

1 the signals that you are measuring are ECG's?

2 DR. SHEN: Correct.

3 DR. RUDY: Okay, thank you.

4 DR. GOODMAN: I'll also just  
5 remind the panel, the electro physiology and  
6 the math is fascinating but do remember that  
7 are questions start with detection and move on  
8 to physician behavior, patient outcomes and so  
9 forth. So the math is great but we don't have  
10 a math question.

11 Further questions at this point  
12 for our panel. Is that Dr. Heseltine?

13 DR. HESELTINE: Yes, one question  
14 for Dr. Shen. You mentioned in your  
15 presentation that your system detected not  
16 only ischemia but other pathology. If we  
17 exclude arrhythmia detections, arrhythmia  
18 pathology what are we left with if it's not  
19 ischemia?

20 DR. SHEN: Hypertrophy can be non  
21 ischemic or ischemic, but it changes the heart  
22 shape. Actually this technology can be used

1 to measure remodeling, gradual remodeling as  
2 a result of a valve disease. For instance  
3 someone has a atrophy of the aorta valve  
4 stenosis over time the left ventricle, will  
5 eventually evolve. And actually the system  
6 can be used to measure that, that measuring  
7 without even having to do with anything with  
8 ischemia.

9 DR. HESELTINE: And that's  
10 different from the 12-lead EKG which also  
11 detects hypertrophy?

12 DR. SHEN: That's different, the  
13 way that's measured, we're measuring entire  
14 different things.

15 DR. HESELTINE: Thank you.

16 DR. GOODMAN: Good, thank you. I  
17 have a question. Starting with out TA people.  
18 Back to kind of a higher order question. We  
19 have pair of questions, actually for us they  
20 are Questions 3 and 4. That deal with the  
21 impact of this type of technology, and  
22 physician decision making.

1                   And if I read the TA correctly you  
2                   found zero studies addressing physician  
3                   decision making. I just want to confirm that  
4                   that is correct.

5                   Okay, do any of our speakers have  
6                   published peer reviewed evidence, not to be  
7                   published or just in an abstract that any of  
8                   these technologies are shown to effect  
9                   physician decision making?

10                  Okay, apparently not, okay, good.  
11                  I just wanted to make sure I understood that.  
12                  I apologize if I'm the only one who wasn't  
13                  sure about that.

14                  And then we have a pair of  
15                  questions in with patient outcomes, for which  
16                  the TA discerned three studies. And if you  
17                  don't mind, can I ask our TA people to come up  
18                  and just briefly recap what those three  
19                  studies were?

20                  And for what technology they  
21                  apply? There were three of them. And chances  
22                  are at least two of them had to be the prime.

1 DR. COEYTAUX: This is Dr.  
2 Coeytaux, my recollection that there are two  
3 studies. Please correct me if I'm wrong, you  
4 have the report, is it three? There may have  
5 been three papers, to OCCULT trials and then  
6 one by, the last name, the first author is  
7 escaping me. Two studies?

8 DR. GOODMAN: Yes, you're right,  
9 there were three papers.

10 DR. COEYTAUX: So very briefly by  
11 memory here, the OCCULT trial is the only  
12 study that published the findings of the data  
13 they collected. And it had to do with looking  
14 at the outcomes of patients who had STEMI as  
15 identified by the prime EKG compared to the  
16 ECG identified STEMI patients.

17 That's the only piece of data that  
18 I think we found, would you like me to repeat  
19 that?

20 DR. GOODMAN: So it was prime  
21 versus the ECG?

22 DR. COEYTAUX: Prime versus the

1 ECG in terms of identifying STEMI, ST  
2 elevations. Identifying ST elevations.

3 DR. GOODMAN: But is that  
4 improving patient outcomes?

5 DR. COEYTAUX: So the reason, I  
6 mentioned before about the mention of limited  
7 evidence. The reason we chose to bring this  
8 to the level of discussion and bringing it up  
9 is because there may be.

10 There's two ways of interpreting  
11 this data as I can see it. There are two, it  
12 may be important data, but I don't know. The  
13 reason we brought this up was because it was  
14 there in the section of the paper that talked  
15 about prognosis, events that happen after the  
16 initial diagnosis.

17 The way I can interpret this data,  
18 the only two ways I think I can think of is  
19 that it's interesting that there's a prime EKG  
20 that identified ST elevation. And they found  
21 that of those people, of those patients there  
22 was significant mortality. There was a bad

1 event associated with it. That's what I would  
2 call it.

3 Whereas the ECG, that identified  
4 an ST elevation there was no such worsening of  
5 outcomes to those people. So there was a  
6 difference, they identified two different  
7 outcomes based on a test at a given period of  
8 time.

9 DR. GOODMAN: That is prognostic  
10 information. Not information about the impact  
11 of diagnostic technology on patient outcomes.

12 DR. COEYTAUX: That's a fair  
13 statement, I think both are fair statement, it  
14 is prognostic but it may be because of  
15 outcomes it may be because. It could be, and  
16 this is where I was getting to about the two  
17 ways of interpreting it.

18 It could be that the prime ECG  
19 identified a different, slightly different  
20 population. They did identify a slightly  
21 different patient population. Some people had  
22 ST elevation on one test and not on the other.

1                   So it could be that the difference  
2                   in population had different prognosis,  
3                   therefore it would be a prognostic issue.

4                   I could also be that a decision  
5                   could have been made, based on the findings of  
6                   the prime ECG, that lead to a change in  
7                   outcome. We don't know.

8                   DR. GOODMAN: But no study that  
9                   you reviewed actually was designed to detect  
10                  a causal relationship between the test and the  
11                  patient outcome?

12                  DR. COEYTAUX: That is absolutely  
13                  true, there's no question about that. This is  
14                  a secondary finding that we chose to elevate  
15                  to the point of this discussion. But it's  
16                  fraught with the potential concerns that you  
17                  are mentioning.

18                  `That it was not designed to do  
19                  this, it was a secondary finding that we  
20                  reported because we found it and we stated  
21                  because it may have implications. But it is  
22                  far too early to conclude one way or the

1 other.

2 DR. GOODMAN: So, let me make sure  
3 I understand this. No study was designed to  
4 detect a causal relationship?

5 DR. COEYTAUX: Absolutely true.

6 DR. GOODMAN: A couple of articles  
7 reported finding that what happened later to  
8 these folks was different?

9 DR. COEYTAUX: Yes.

10 DR. GOODMAN: But there's  
11 absolutely no evidence that that had anything  
12 to do with their having had a test or not?

13 DR. COEYTAUX: There is no valid  
14 evidence, there is just, yes, I certainly  
15 agree. It is in a report that there were  
16 outcomes that differed.

17 And the study was not defined,  
18 designed to look at this, there's no causality  
19 that can be definitively inferred. But the  
20 data were there and we're presenting it for  
21 discussion.

22 But it a very weak level of

1 evidence. And it is one that has inherent  
2 bias for the reasons that you're mentioning.

3 DR. GOODMAN: I think you made a  
4 generous inference there but we appreciate  
5 your inclusivity. Thank you.

6 DR. COEYTAUX: You're welcome.

7 DR. GOODMAN: I believe that's Dr.  
8 Imhoff, sir. On this issue? Thank you. Dr.  
9 Imhoff, you're about two meters tall so I  
10 don't know if you want to bend down or lift  
11 the mic, but we want to make sure, either way  
12 we want to make sure we hear you.

13 DR. IMHOFF: I'm just speaking out  
14 loud so I think that you can hear me. I just  
15 want to make a very general comment about the  
16 diagnostic test, or the general diagnostic  
17 test that we are looking at.

18 Diagnostic tests as such cannot  
19 have any impact on outcome with the exception  
20 of direct complications from a diagnostic test  
21 for coronary angiography. It can only have  
22 impact on outcome if a therapeutic decision is

1 influenced by this test.

2 And then this decision is also  
3 enacted in therapy and therefore none of the  
4 studies that I'm aware of would fit into the  
5 category.

6 DR. GOODMAN: Thank you, sort of  
7 Dr. Imhoff. I appreciate your view point, I  
8 don't agree with your finding. There are many  
9 cases where screening tests or diagnostic  
10 tests a study of those has been designed to  
11 follow a set of patients, whether it's in an  
12 RCT or some other study where a causal finding  
13 can be made.

14 That's why we do these tests is  
15 because we want to improve patient outcomes.  
16 Ultimately we appreciate that the relationship  
17 may be indirect from time to time.

18 But we're looking at the questions  
19 asked here and I think it's been confirmed  
20 that nothing was found about influencing a  
21 decision.

22 And it sounds like nothing was

1 found about improving a patient outcome from  
2 a causal standpoint. However hard that may  
3 have been to establish, it doesn't appear that  
4 anything was found.

5 Did the gentleman from the TA have  
6 anything to say on that? You started to  
7 approach the mic but I think now you've took  
8 your seats again. If it's really important  
9 we'd be glad to hear it.

10 MR. LEISY: Philip Leisy again.  
11 It's on this same issue that we've been  
12 talking about. It goes back to the OCCULT  
13 trial, when we looked at patient outcomes and  
14 they're finding was that the 80 lead only ST  
15 elevation patients versus the 12-lead only ST  
16 elevation patients.

17 The door-to-sheath time, or the  
18 time between presentation of symptoms and  
19 intervention, was much greater for the 80 lead  
20 only ECG.

21 The time difference if I could  
22 find in here, was for the 12-lead only, for

1 the 80 lead only was greater than 1,000  
2 minutes, door to intervention.

3 And with the ECG 12-lead only was  
4 less than 60 minutes, 54 minutes. So that  
5 could potentially be, while they did not  
6 attribute the poor outcomes to that finding  
7 that was a finding in the result of that  
8 report.

9 DR. GOODMAN: Okay. So it's  
10 possible that in that study, which may or may  
11 not have been designed, to detect that  
12 difference that you just cited. That perhaps  
13 action was taken more rapidly in one instance  
14 than another?

15 MR. LEISY: Correct.

16 DR. GOODMAN: Perhaps, and that  
17 doesn't mean that one can confer that having  
18 taken that action any faster or slower might  
19 have effected the patient outcome?

20 MR. LEISY: Right.

21 DR. GOODMAN: It's possible,  
22 possible it might have reflected a change in

1       clinician decision making. Again just  
2       possible, the studies weren't designed to  
3       detect that I don't think.

4               MR. LEISY: Correct.

5               DR. GOODMAN: Okay, thank you for  
6       noting that. That's very helpful for us.

7               MR. LEISY: You're welcome.

8               DR. GOODMAN: We'll take one more  
9       question before the lunch break, Dr. Janowitz.

10              DR. JANOWITZ: I just want to ask  
11       anyone on the panel if anyone has data  
12       concerning use of this technology in  
13       asymptomatic patients?

14              DR. GOODMAN: No one is  
15       approaching the microphone Dr. Janowitz.  
16       Thank you. Dr. Phurrough?

17              DR. PHURROUGH: I was going to ask  
18       this question too. In your slide ten Dr  
19       Imhoff, you specify MCG was validated in  
20       patients with indication for coronary  
21       angiography including asymptomatic patients.  
22       So that seemed to be a positive to Dr.

1 Janowitz question?

2 DR. IMHOFF: Yes, but I refrain  
3 from answering that question because we did  
4 not explicitly analyze that sub-pool.  
5 Therefore we have no data to present on  
6 asymptomatic patients only. And I think that  
7 was the question.

8 We had a mix of patients that were  
9 symptomatic A. Symptomatic were scheduled for  
10 coronary angiography so chronic CAD with or  
11 without symptoms. So I cannot say anything  
12 statistically relevant about this subgroup  
13 asymptomatic patients.

14 DR. GOODMAN: Okay, thank you.  
15 Dr. Coeytaux, if you could approach the mic  
16 just one more time. I just want to make sure  
17 I understand this. On the asymptomatic. I'm  
18 sorry to be redundant about this.

19 You stated earlier that your  
20 search strategy was not designed to exclude  
21 asymptomatic patients? So in your judgement  
22 you would have captured studies on

1 asymptomatic patients had they been in there?

2 And however it's possible that the  
3 people that were doing hand searches might  
4 have set a study of that type aside. I think  
5 you said it was unlikely but it's a possible,  
6 is that correct?

7 DR. COEYTAUX: That is correct.  
8 If I might take one minute to expand upon it,  
9 because it is such an important question.  
10 That is correct, everything you said, I agree  
11 with entirely.

12 But I do want to say that we  
13 approached this task with a clinical scenario  
14 in mind of this technology being used to  
15 assess patients in real time who might have  
16 ischemic heart disease. Therefore that is the  
17 mind set, that is what we did.

18 The study on the search strategy  
19 absolutely included the whole universe of  
20 patients who could fall into any of these risk  
21 groups. In the second stage, so I'm very  
22 confident that we did not exclude anything

1 structurally by the search values. I'm  
2 confident about that.

3 But going forward from there in  
4 deciding and applying the criteria and looking  
5 at the titles and then further at the full  
6 text review.

7 I certainly and I believe all my  
8 colleagues are who also were doing this were  
9 thinking in the clinical scenario of patients  
10 who have some reason to be evaluated for  
11 ischemic heart disease. That's how we went  
12 through this.

13 Now we had further discussions  
14 afterwards about making sure that question of  
15 asymptomatic on patients was addressed in  
16 preparation for this meeting.

17 So what we did then is we went  
18 back to our search strategy, we looked at the  
19 group I think of 58 studies that had been  
20 excluded for patient population. Looked very  
21 carefully at those to see if we excluded for  
22 asymptomatic reason, and we did not.

1 DR. GOODMAN: You took a step to  
2 actually go back and see if yo had done that?

3 DR. COEYTAUX: We did take that  
4 step. We did officially take that step which  
5 is a little bit out of protocol because we had  
6 already gone through that process.

7 But since we had already, since we  
8 routinely and by protocol separate out the  
9 reasons why, identify why we excluded studies.  
10 We had a category of not population of  
11 interest.

12 So I personally went back to all  
13 58 of those and looked at those to see if  
14 maybe we had, for whatever reason, excluded  
15 for reasons of asymptomatic. And there were  
16 none.

17 And that gives me great confidence  
18 to say I really don't think that in the entire  
19 body of studies that we first collected in the  
20 2,000 or so that I'm very confident that none  
21 of those have asymptomatic patients.

22 DR. GOODMAN: Okay. Thank you

1       very much. Panel this happens from time to  
2       time, given the time difference between when  
3       for when CMS asks for an assessment to be  
4       done and when we actually have our meeting can  
5       six months, eight months. Sometimes a year or  
6       more.

7               So we do need to acknowledge a bit  
8       of a disconnect between the questions that  
9       were asked of the TA folks and the questions  
10      that we're asked to answer.

11             So we've been trying to extract  
12      whatever we could at this point about that  
13      issue on our Question 1a and 2a and so forth  
14      about asymptomatic patients. So I think we  
15      have an imperfect answer to this but a  
16      partially useful one.

17             With that let's take our lunch  
18      break. I hope you don't mind, we've stolen  
19      six and a half minutes from your lunch.  
20      Let's, never the less, meet here at 1:00 p.m.

21             Thank you, this has been a very  
22      helpful morning to all of our speakers,

1 panelists we very much appreciate your  
2 information and attention. See you at one.

3 (Whereupon, the above-entitled  
4 matter went off the record at 12:08 p.m. and  
5 resumed at 1:02 p.m.)

6 DR. GOODMAN: We will get started,  
7 I'll ask again if the folks who've been our  
8 presenters and our TA folks could come to the  
9 front of the room it would be helpful.

10 As noted before we do have this  
11 main job of our panel does, of answering these  
12 ten questions. The four times two plus the  
13 two questions.

14 And I think we will probably  
15 proceed to get into the questions pretty soon.  
16 But before that I think we've got some  
17 clarifications we may want to make here.

18 And if I can pick on Dr.  
19 Phurrough, if he doesn't mind, one of the  
20 issues, Dr. Phurrough that came up was perhaps  
21 a need for clarifying matters of asymptomatic  
22 and some other definitions.

1           Have you, starting really with the  
2           first question. Did you want to clarify that  
3           for us, or pose that for us?

4           DR. PHURROUGH: Well, I think I  
5           understand asymptomatic versus with and  
6           without chest pain. I think there's been some  
7           lack of clarity between what we've heard from  
8           the TA and what we've heard from the various  
9           presenters and what the questions actually  
10          are.

11          So I think it would be helpful for  
12          Dr. Rollins or Dr. Miller or someone to try  
13          and clarify for us the differences in A and B  
14          just to make sure that we're clear and then  
15          that may lead to a couple more questions to  
16          the presenters.

17          DR. GOODMAN: Okay, and when you  
18          say A and B you mean for example in Question  
19          1a being, reliably and accurately detect  
20          coronary artery disease in asymptomatic  
21          patients at risk for the disease.

22          And B, patients with signs and

1 symptoms suggestive of ACS with or without  
2 chest pain. That distinction? Okay.

3 And I'm going to give a little  
4 heads up to Dr. Steinbrook, who I think was,  
5 needed a bit of clarification about whether  
6 we've got a comparator here or not. So Dr.  
7 Steinbrook, you're on notice for raising that  
8 issue.

9 Let's get started here, McDonough  
10 coming pretty soon. Dr. Rollins and or Dr.  
11 Miller?

12 DR. ROLLINS: I'll go ahead and  
13 get start. In terms of A, coronary artery  
14 disease in asymptomatic patients at risk for  
15 disease. That would be an individual who does  
16 have CAD but they're void of any symptoms.

17 They have no chest pain, they may  
18 not even have any symptoms, other signs of CAD  
19 such as shortness of breathe or dyspnea or  
20 other types of characteristics.

21 Whereas B, patients with sign and  
22 symptoms suggestive of ACS with or without

1 chest pain. That would be a patient with  
2 acute coronary syndrome, some with chest pain  
3 and some without chest pain.

4 Those without chest pain would  
5 still have the other symptoms related to CAD  
6 such as shortness of breath and those other  
7 types of activities associated with those  
8 conditions.

9 DR. GOODMAN: And let me also  
10 note, because you do put in the preamble of  
11 our questions that B specifically talks about  
12 low and intermediate risk. Patients at low or  
13 intermediate risk. Yes, Dr. Miller?

14 DR. MILLER: We have for B, we are  
15 looking at patients with signs and symptoms  
16 suggestive of ACS who are not triaged for  
17 emergent reperfusion therapy.

18 As we were thinking of those  
19 patients we were using the American Heart  
20 Association, 2010, I think it is guidelines  
21 That have been previously mentioned. In which  
22 the American Heart Association divides

1 patients into three categories should they  
2 come into your medical facility for symptoms  
3 of ACS.

4 So STEMI patients or STEMI  
5 equivalent patients are those that are  
6 assigned a very high risk by the American  
7 Heart Association. And it is advised that  
8 within a very short period of time they are  
9 prepared and initiated to have a some sort of  
10 reperfusion therapy.

11 So those patients would not  
12 necessarily have further testing done upon  
13 them than the usual 12-lead ECG and then there  
14 would be a decision point and they would go  
15 off to their therapy.

16 For those patients who have  
17 unstable angina, non-STEMI's non-diagnostic  
18 ECG and what am I forgetting here. And a  
19 normal ECG but who have a reasonable history  
20 of ACS like symptoms. It would be very likely  
21 that they would have other testing done.

22 So that is the population that we

1 are talking about today when we say that they  
 2 have low to intermediate risk and the  
 3 corollary of that for us was that they would  
 4 not be immediate candidates, or I'm sorry,  
 5 urgent candidates for reperfusion therapy.

6 DR. GOODMAN: Dr. Phurrough?

7 DR. PHURROUGH: Just a bit more  
 8 clarity on asymptomatic. Let me just ask, are  
 9 we talking about patients who have never had  
 10 any symptoms, related to coronary artery  
 11 disease?

12 DR. MILLER: Yes.

13 DR. PHURROUGH: Or patients who  
 14 are currently asymptomatic but may have had a  
 15 diagnosis previously?

16 DR. MILLER: No, we are talking  
 17 about absolutely no symptoms but you have a  
 18 high, they have high risk and you, their  
 19 physician, has high suspicion of the fact that  
 20 they may have coronary artery disease.

21 DR. PHURROUGH: But not based on  
 22 symptoms?

1 DR. MILLER: Not based on  
2 symptoms.

3 DR. PHURROUGH: So with that  
4 definition, are any of the patients that have  
5 been included in the studies that we're  
6 talking about today fit that category?

7 DR. GOODMAN: This is Dr.  
8 Strobeck.

9 DR. STROBECK: Yes, I've had  
10 patients come to me for evaluation of an  
11 abnormal EKG for example. The development of  
12 a right bundle branch block who participated  
13 in my trial because there was a concern on the  
14 part of a referring physician that this  
15 patient may have underlying coronary disease  
16 but they've had no symptoms whatsoever.

17 The abnormal EKG is difficult  
18 sometimes to evaluate using traditional stress  
19 testing methods and we found that the MCG was  
20 very helpful because it would. The accuracy  
21 is independent of the EKG morphology. So  
22 those patients were in there.

1 DR. PHURROUGH: So there were  
2 patients who had an abnormal ECG and agreed to  
3 enroll. Never had symptoms, agreed to enroll  
4 in your trial, and had either ECG or SPECT and  
5 then went on to CAD?

6 DR. STROBECK: Went on CAD if the  
7 SPECT was abnormal.

8 DR. PHURROUGH: If the SPECT was  
9 abnormal. Okay.

10 DR. GOODMAN: So Dr. Phurrough,  
11 are you satisfied that you got a good answer  
12 to your question?

13 DR. PHURROUGH: I have the answer,  
14 yes.

15 DR. GOODMAN: Hold on, Dr. Seal.  
16 Dr. McDonough is your question pursuant to  
17 this point or a different one? Okay. Then  
18 we'll return to you. Dr. Seal, is yours about  
19 this point?

20 DR. SEAL: Yes, it's about the  
21 same population, so is this was the single  
22 center, 116 patients?

1 DR. STROBECK: Correct.

2 DR. SEAL: How many patients were  
3 asymptomatic of 116?

4 DR. STROBECK: There was just a  
5 handful, probably ten to 15 patients.

6 DR. GOODMAN: Okay. Thank you, on  
7 this point, it was initiated by Dr. Janowitz.

8 DR. JANOWITZ: It seems to me  
9 we're excluding a large group of patients who  
10 are not acute coronary syndromes but who  
11 present to their doctor with either atypical  
12 chest pain or some symptoms suggestive of  
13 heart disease.

14 And those seem to be the majority  
15 that goes for the noninvasive testing and  
16 stress testing. How do those not fit under  
17 that A's please clarify?

18 DR. GOODMAN: The A's are coronary  
19 artery disease to detect CAD in asymptomatic  
20 patients at risk for disease.

21 DR. JANOWITZ: Right, but most --  
22 many of them are symptomatic. And they don't

1 fall under B either.

2 DR. GOODMAN: Well, B I would take  
3 as patients who are presenting to the  
4 emergency room with suspected acute coronary  
5 syndrome.

6 DR. MILLER: I'm sorry, I should  
7 have clarified. The B patient we are  
8 considering is if they did have symptoms,  
9 someone comes in to you says last night I was  
10 short of breath for 30 minutes and I rested it  
11 went away, I'm fine. Okay. That patient we  
12 would put under B. Okay? I'm sorry I wasn't  
13 clear.

14 DR. GOODMAN: Thank you, Dr.  
15 Miller, just to remind folks. This is Dr.  
16 Heseltine.

17 DR. HESELTINE: So, Dr. Miller,  
18 when you started to describe Group A, I  
19 thought I understood quite clearly that these  
20 were asymptomatic patients. And that they  
21 didn't have findings other than broad  
22 findings.

1                   But then I watched your face as we  
2                   discussed the issue of abnormal  
3                   electrocardiogram but non-diagnostic. Where  
4                   are you placing those patients?

5                   DR. MILLER: For example, the  
6                   example that Dr. Strobeck gave. We had not  
7                   considered that, personally I would put them  
8                   in B. I would consider the abnormal ECG as  
9                   being a potential sign or symptom of  
10                  significant coronary artery disease.

11                  DR. HESELTINE: Yes, but you say  
12                  ACS is the definition.

13                  DR. MILLER: Right, you're  
14                  absolutely right.

15                  DR. HESELTINE: And that's a  
16                  syndrome and either you have it or you don't.  
17                  Most people might make the argument that  
18                  somebody comes in even with a left bundle  
19                  branch block isn't necessarily somebody with  
20                  ACS.

21                  DR. MILLER: Yes, so I think, to  
22                  be perfectly honest we hadn't considered that

1 group of people.

2 DR. GOODMAN: Okay. In the  
3 preamble to the questions though for the B's  
4 which correspond to the preamble Number 2, in  
5 patients who present with signs or symptoms of  
6 ACS, with or without chest pain.

7 It also says of low or  
8 intermediate risk for ACS which is thereby  
9 defined, thereafter defined as signs or  
10 symptoms of MI and 12-lead ECG demonstrating  
11 unstable angina non ST elevation, MI or  
12 nondiagnostic.

13 So there are going to be, for the  
14 definition of low or intermediate risk for ACS  
15 signs or symptoms of MI and those other  
16 things.

17 So I think that helps draw the  
18 line a little bit more clearly. Dr.  
19 McDonough, next on this?

20 DR. MCDONOUGH: Sure, on a  
21 different issue about the same question.

22 DR. GOODMAN: Okay, we cool with -

1       - are we okay with this part of the question  
2       so far? Steve, back to you, he's nodding his  
3       head. Dr. Heseltine, close enough at this  
4       point?

5                   DR. HESELTINE: I don't, to your  
6       point I think a substantial number of patients  
7       are being excluded by both questions. If you  
8       don't have ACS, and you have abnormalities, it  
9       seems to me that they could be included in A.

10                   And if that's where you want to  
11       put them that's fine. But what I'm hearing is  
12       a variety of people putting them B or A.

13                   DR. GOODMAN: Okay. When it comes  
14       time to answering our questions if there is  
15       some grey area there aside from any vote you  
16       may offer? We'll take your comments to  
17       accompany those because we want the agency to  
18       have those clarifying discussion points as  
19       they go forward. Thank you.

20                   Dr. McDonough, thank you for your  
21       patience.

22                   DR. MCDONOUGH: I'm looking at

1 Question 1b, and it appears there is, maybe  
2 it's obvious but I want to make it absolutely  
3 clear. There is a word or a phrase that's  
4 missing.

5 "Are able to reliably and  
6 accurately detect, what, in patients with  
7 signs and symptoms of acute coronary  
8 syndrome."

9 Is it coronary artery disease  
10 which is an anatomic diagnoses or is it  
11 myocardial ischemia or is it necrosis,  
12 myocardial necrosis? What are we talking  
13 about?

14 DR. GOODMAN: Let me offer this.  
15 I think the answer to that is you are correct.  
16 The question is not worded accurately, but the  
17 preamble which explains why these questions  
18 are being ask does.

19 The preamble which starts the  
20 second paragraph, the questions below refer to  
21 the use of, et cetera. It says for the  
22 purpose of detecting CAD in 1, patients who

1 are asymptomatic, 2, in patients who present.

2 So what 1b should say is, coronary  
3 artery disease in patients with signs and  
4 symptoms.

5 DR. MCDONOUGH: Coronary artery  
6 disease?

7 DR. GOODMAN: Yes, because the  
8 transposition from Paragraph 2 in the  
9 preamble, to the wording of the Question 1b  
10 did not pick up the phrase CAD. In both  
11 instances, when it should have. At least  
12 that's my understanding of the intent of the  
13 questions.

14 And I don't see Dr. Miller  
15 disagreeing. Thank you for picking that up,  
16 a good grammar teacher would have detected  
17 that as well. Dr. Janowitz.

18 DR. JANOWITZ: I hate to be nit  
19 picky about this but I would request that we  
20 say obstructive coronary artery disease.  
21 Because many people have non obstructive  
22 coronary disease.

1 DR. GOODMAN: Okay. That is a  
2 very good point to make and I will defer to  
3 some of our cardiologist friends. Because we  
4 did see different forms of CAD in our  
5 presentations today.

6 I think we saw spasms, and we saw  
7 things other than the blockage, correct? Dr.  
8 Rollins and or Dr. Miller, what is your,  
9 what's your intent on this? CAD, is CAD  
10 confined to, what blockages to use the  
11 colloquial term, or the other forms of CAD?  
12 You can think about that for a moment, or  
13 confer.

14 DR. HESELTINE: Can I add to that  
15 question?

16 DR. GOODMAN: Go right ahead, Dr.  
17 Heseltine.

18 DR. HESELTINE: It seems to me  
19 that dancing around the word usage here, which  
20 comes from different disciplines. Actually  
21 obstructs the purpose of this. Which is why  
22 are we investigating these patients at all?

1                   And essentially I would think that  
2                   it's to either, diminish, prevent, or  
3                   alleviate ischemia. Which eventually might go  
4                   on to damage the heart, and obviously does.

5                   So it seems to me that that's  
6                   where everything, if you'll pardon the pun,  
7                   flows from. So I would include the real  
8                   meaning here of the intent. I interpreted the  
9                   intent to mean what we're driving at is can we  
10                  use these systems to detect patients who are  
11                  either ischemic or likely to be ischemic or  
12                  could become ischemic soon.

13                 DR. GOODMAN: So the broader  
14                 definition of CAD. As opposed to the more  
15                 narrowly defined. Dr. Miller is nodding her  
16                 head, and Dr. Rollin's is also nodding his  
17                 head. It seems as though the agency would  
18                 concur.

19                 Thank you, Dr. Janowitz for  
20                 bringing up that point. This is all  
21                 necessary, we have to nail this all down. Dr.  
22                 Steinbrook, sir.

1 DR. STEINBROOK: Thank you, I have  
2 a slightly different question, but about the  
3 same set of questions, 1 and 2. So it says  
4 these technologies were able to reliably and  
5 accurately detect CAD. So what is the  
6 standard of comparison here?

7 In other words, if we're thinking  
8 about these in the context of the standard EKG  
9 I might think about this differently than if  
10 the standard of comparison is coronary  
11 angiography.

12 It would be helpful to have, and  
13 some of the studies which were reviewed in TA  
14 were looking against standard EKG's. So it  
15 would be helpful to have some clarity as to  
16 what you're trying to get at with this  
17 question.

18 DR. GOODMAN: And Dr. Miller, if  
19 you and or Dr. Rollins might approach that.  
20 Just in one word we're wondering if you've got  
21 a comparator in mind. And if so, is that ECG  
22 or is just against nothing, versus nothing.

1 DR. MILLER: I think the key to  
2 that question is in Number 5, or to your  
3 question, Dr. Steinbrook.

4 In question Number 5 we are asking  
5 whether or not there is any incremental  
6 information obtained from these new  
7 technologies, beyond that that is provided by  
8 the ECG. This is the 12-lead standard ECG.

9 DR. STEINBROOK: So in thinking  
10 about how we would respond to Questions 1 and  
11 2 we should basically read them as if Question  
12 5 even thought that's not actually the wording  
13 here?

14 DR. MILLER: Well, one and two  
15 have to do with, do you believe that the SAECG  
16 technology, as a stand alone, is able to  
17 reliably and with validity, and accurately  
18 detect coronary artery disease, myocardial  
19 ischemia in these two sets of circumstances,  
20 compared. Do you believe that it is possible  
21 to do that clinically at this stage in time?

22 DR. STEINBROOK: That's really,

1       then comparative just for Questions 1 and 2 is  
2       nothing.

3                   DR. MILLER:   Right.

4                   DR. STEINBROOK:  Not anything  
5       else?

6                   DR. STEINBROOK:  Okay.  That's  
7       very helpful because it was for the reasons I  
8       stated it was unclear to me how we should be  
9       doing the question.

10                  DR. GOODMAN:  Okay.  Good, so the  
11       comparator is nothing in particular at this  
12       time.  Although we would anticipate by the  
13       time we get to Question 5 that the marginal  
14       difference would be of interest.  But for one  
15       and two it is not.  Thank you, excellent.  Dr.  
16       McDonough.

17                  DR. MCDONOUGH:  Just also for  
18       clarification, I hate to pick on things.

19                  DR. GOODMAN:  Go right ahead, Dr.  
20       McDonough.

21                  DR. MCDONOUGH:  Are we going to  
22       vote on different technologies?  I mean, my

1       answer on say vector cardiography, may be  
2       different than body surface potential mapping.  
3       Or are we thinking of these just in general?  
4       These technologies, one vote.

5               DR. GOODMAN:   Given the scope of  
6       the evidence.   Well first of all, given the  
7       scope of the evidence it appears that we've  
8       got peer review literature on just a couple of  
9       them.   Two of these, ten studies on one and  
10      one study on the other.

11              So our n is pretty small, I would  
12      say that our deliberations will be reflected  
13      in two ways.   One the vote, two the discussion  
14      points.

15              And I would recommend that if the  
16      questions about adequacy of evidence, what the  
17      evidence demonstrates.   As long as there's  
18      adequacy of evidence for at least one, you can  
19      vote that way.   And proceed thereafter.   But  
20      our discussion will make clear to which we  
21      were referring.   Okay?

22              But I'm glad you ask the question,

1       it's not kind of average or kind of the net  
2       overall, if at least one of these things is  
3       hitting buttons someplace we'll want to know  
4       about, you can vote that way.

5               Unless, I don't see any  
6       disagreement on that. Hello, Dr. Miller.

7               DR. MILLER: Correct me if I'm  
8       wrong but the TA limited itself to body  
9       surface mapping, and those signal analysis  
10      technologies that used a mathematical  
11      conversion. And if you give me a second we  
12      can look that up in the TA.

13              DR. GOODMAN: Well, allow me to  
14      interject, the preamble, defines SAECG  
15      technologies as one, assess electrical  
16      activity to the heart. Two, transform or  
17      interpret the signal through spacial imaging  
18      or advanced mathematical modeling.

19              DR. MILLER: Right, so the -- did  
20      you include any, and I'm addressing this to  
21      the writers of the TA. Did you include any  
22      other technologies outside of the body surface

1 mapping in terms of the spacial imaging?

2 MR. LEISY: Philip Leisy here to  
3 answer. Yes, we did include each of the  
4 technologies and devices that were shown in  
5 that table above in the presentation that had  
6 about 12 or so different devices.

7 So we did include the signal  
8 average ECG which is that the LP3000, the body  
9 surface mapping. We included the mathematical  
10 analysis, which is the 3DMP, we also included  
11 vector cardiography. There are two devices  
12 that had vector cardiography.

13 And there were also the HYPERQ  
14 ECG's as well were included. The only reason  
15 that none of those other technologies  
16 reproduced studies because none of the studies  
17 fit the inclusion criteria.

18 DR. GOODMAN: Thank you. Can I  
19 call Dr. Louis Jacques to the microphone  
20 please?

21 DR. JACQUES: Hi, I'm Louis  
22 Jacques, J-A-C-Q-U-E-S. Just to reenforce

1        what you said, many times, for MEDCAC's what  
2        is more informative than any particular voting  
3        numerical result are the actual conversations  
4        around that. We do not currently have an open  
5        national coverage determination on any one of  
6        these proprietary technologies now.

7                    And based on what I've heard  
8        during this morning and parts of this  
9        afternoon in fact, the greatest value of some  
10       of your deliberations or comments may be to  
11       specifically highlight areas where you may  
12       like to see more.

13                   So in that result -- nobody's  
14       going to die based on your vote. Okay? So if  
15       you believe that based on any of these  
16       technologies that you feel confident enough to  
17       name a particular score, feel free to do so.

18                   Because we will find from your  
19       comments about your vote whether you were  
20       really aiming at one or the other or a more  
21       general statement.

22                   DR. GOODMAN: Thank you for that

1 clarification, Dr. Jacques. All right. Any  
2 other questions, and just a little bit of  
3 warning here. I sense that pretty soon we are  
4 actually going to start answering these  
5 questions. Not just at this moment.

6 Just kind of a preamble or just  
7 kind of explanation of how it's going to go.  
8 Is that as we approach each question, we're  
9 not going to dive into the Likert scale  
10 grading right away.

11 I will probably want to ask the TA  
12 team to provide a synopsis, a real distilled  
13 synopsis on what they found relative to the  
14 question that's going to be on the table at  
15 the time. So we're going to want your kind  
16 of, you know, highlights here.

17 And then we might also call upon  
18 any of our other speakers who are highly  
19 confident that they have an important point to  
20 make on that particular question that we as  
21 voting -- that our voting members need to  
22 know.

1                   So just a little warning that once  
2 we get into voting, it doesn't mean you are  
3 off the hook. Especially you TA people, I'm  
4 going to ask you to think ahead about a  
5 synopsis reach. Got it? Good, thank you.  
6 Dr. McDonough?

7                   DR. MCDONOUGH: Dr. Strobeck  
8 presented a study which was not included in  
9 the TA but would have met inclusion criteria.  
10 I haven't reviewed it other than what we've  
11 been presented. Do we consider it?

12                  DR. GOODMAN: This was the study  
13 that the TA folks thought would have met there  
14 inclusion criteria but was published this  
15 year. So recently that it predated the time  
16 of your work.

17                  Again since we're not voting on  
18 the issue. Dr. Rollins, did you want to  
19 comment?

20                  DR. ROLLINS: Even though this  
21 article has been published, I guess since our  
22 information went out, did everybody have

1 access to it? And was able to read it?

2 DR. GOODMAN: No. That's what I'm  
3 coming to. So what we need to do is  
4 acknowledge that the study exists, we've heard  
5 a little bit about it. But we don't have it  
6 in front of us. So I don't think that that's  
7 going to weigh very heavily.

8 We cannot tell you to not consider  
9 that, as an individual from public or private  
10 sector who's making some judgement here. But  
11 if it's not in front of you and not in the  
12 evidence table you probably have less to go  
13 on there.

14 DR. ROLLINS: And also you don't  
15 have the capacity without seeing it, to  
16 actually assess it and take a look at it and  
17 make sure that the, you know, from an  
18 evidentiary perspective that the methodology  
19 was correct in, you know, those type things.

20 DR. GOODMAN: Right, so that's  
21 just an adherent kind of problem we have  
22 sometimes. It's a matter of lag time. But I

1 was the chair can't tell you to not think  
2 about it if you so choose. Dr.  
3 Cabral-Daniels.

4 MS. CABRAL-DANIELS: Just a point  
5 fo clarification, did I understand that the  
6 technology assessment folks said that it may  
7 likely have met the criteria. But was a  
8 definitive decision made on that?

9 DR. GOODMAN: Yes, as everyone  
10 recalls the TA folks did a quick look at the  
11 article. The hard copy that was handed to  
12 them late this morning.

13 DR. COEYTAUX: Yes, and I  
14 neglected to say the publication date, which  
15 was October, so just very, very recently came  
16 out.

17 DR. GOODMAN: October 2011?

18 DR. COEYTAUX: 2011, yes, October  
19 2011.

20 DR. GOODMAN: That would be  
21 recent.

22 DR. COEYTAUX: Yes, and our search

1 actually went into October, the Medline search  
2 so it was right outside -- we thought we had  
3 a very recent one but there is still some time  
4 that elapsed.

5 Both of us looked at it quickly  
6 and it looks as though it would be included.  
7 But I do want to highlight that I wouldn't  
8 even be able to make that determination now  
9 even spending more time because we have to go  
10 through an independent process of two  
11 individual independent decisions to be made.

12 So I think it's likely, as you  
13 said, yes, to the likely, but I can't attest  
14 to the certainty of that.

15 DR. GOODMAN: Thank you. And I'll  
16 just remind everyone of Dr. Rollins comments  
17 a moment ago about, it's not in evidence until  
18 you can rigorously assess its quality and so  
19 forth.

20 Okay, other kind of general  
21 questions before we kind of move, before we do  
22 move to the questions themselves? Is there

1 anything that should be on the table that's  
2 off. Are we missing an important piece or  
3 type of evidence? Any kind of clarification  
4 on important matters of definition here? Dr.  
5 Saadi, and please speak directly into the  
6 microphone.

7 DR. SAADI: Sorry, just the same  
8 question again. Dr. Miller, actually it's for  
9 you. The Questions Number A right? When is  
10 asymptomatic patients that at risk for the  
11 disease so they just would be in our elevated  
12 LDL and all these other things and you know,  
13 the averages of smoking. Do want us to  
14 consider those? Is that what is the  
15 definition of the risk?

16 DR. MCDONOUGH: Yes, someone who  
17 would be at high risk for coronary artery  
18 disease as you would define it as practicing  
19 clinician. So for example, someone who has  
20 diabetes, yes.

21 DR. SAADI: Okay. Thank you.

22 DR. GOODMAN: All right then,

1 we're going to proceed now to Question 1. And  
2 recall that this is one of our adequacy  
3 questions, it's not a question of whether  
4 something works or not, it has to do with what  
5 you think of the adequacy of the evidence on  
6 that issue. And we'll take them, 1a, followed  
7 by 1b.

8 And do recall now given somewhat  
9 of a clarification. Question 1 is "How  
10 confident are you that there is adequate  
11 evidence to determine whether or not SAECG  
12 technologies" Could be any of them remember?  
13 "Are able to reliably and accurately detect  
14 1a, coronary artery disease in asymptomatic  
15 patients at risk for the disease." And  
16 remember that this adequacy is not with regard  
17 to a particular comparator? That was a  
18 clarification.

19 Now before we do the voting, I'm  
20 going to ask our TA folks if they could, if  
21 possible, I know this is kind of tough to do  
22 on the run here. If you could summerize, as

1 well as you can, what you found regarding 1A?  
2 Asymptomatic patients and so forth.

3 MR. LEISY: Certainly, so in our  
4 task, we were tasked to identify these two  
5 very different patient populations. The one  
6 the coronary artery disease which is an  
7 anatomical problem as Dr. McDonough addressed  
8 earlier. And the ACS which is the a  
9 physiological representation of the anatomical  
10 problem.

11 Now with 1a, coronary artery  
12 disease and asymptomatic patients, we did not  
13 find very many studies. None of the included  
14 studies included coronary artery disease  
15 specifically. They all addressed acute  
16 coronary syndrome.

17 DR. GOODMAN: None addressed --

18 MR. LEISY: Specifically none of  
19 them addressed coronary artery disease at  
20 presentation. Each patient had a suspicion of  
21 acute coronary syndrome.

22 DR. GOODMAN: Okay. But it was

1 none?

2 MR. LEISY: Correct.

3 DR. GOODMAN: Okay. Any comments  
4 from our speakers, laser-pointed on that  
5 issue, 1a? It looks like Dr. Strobeck is  
6 approaching the microphone.

7 DR. STROBECK: Yes, again, I tend  
8 to agree with Dr. Janowitz, it's very  
9 difficult to find a population of people that  
10 are at high risk that are absolutely 100  
11 percent asymptomatic.

12 Somebody will have an atypical  
13 discomfort or have an abnormal EKG. So the  
14 study that I spoke of specifically included  
15 patients who would have otherwise been  
16 considered asymptomatic.

17 DR. GOODMAN: And that was the  
18 most recently published.

19 DR. STROBECK: The most recent  
20 trial comparing MCG to SPECT.

21 DR. GOODMAN: And that was just  
22 about it, huh? That's about all it got to go

1 on even from your?

2 DR. STROBECK: Yes, I have not  
3 done a study specifically dealing with  
4 absolutely asymptomatic people. I thought  
5 that was a screening test and I didn't think  
6 that the purpose of this would be for  
7 screening.

8 DR. GOODMAN: It's asymptomatic  
9 but having increased risk factors for CAD.  
10 Thank you doctor. Any comments on our  
11 panelists about 1a? Adequacy of evidence.  
12 CAD, asymptomatic patients versus no  
13 comparator in particular. Dr. Steinbrook?

14 DR. STEINBROOK: To clarify, are  
15 we voting on 1a and 1b separately?

16 DR. GOODMAN: Yes, we're going to  
17 vote on 1a and 1b separately. Okay. Ms.  
18 Ellis, did you want to remind us about how we  
19 push buttons or anything like that?

20 MS. ELLIS: Basically all you have  
21 to do is push any number one through five.  
22 For your voting scores, you can press it as

1 many times as you want but the last push will  
2 be the recorded score.

3 DR. GOODMAN: Okay. So Likert  
4 scale, one is low confidence, five is high  
5 confidence, three is intermediate confidence.

6 How confident are you that there  
7 is adequate evidence to determine whether or  
8 not SAEKG technologies are able to reliably  
9 and accurately detect coronary artery disease  
10 in asymptomatic patients at risk for the  
11 disease.

12 One is low confidence, five's high  
13 confidence. And what will happen is once we  
14 have a vote from everyone then the results  
15 magically appear on the screen. This machine  
16 sure makes a lot of noise.

17 MS. ELLIS: I was told that CMS is  
18 working on getting a quieter projector soon.

19 DR. GOODMAN: But we can't wait  
20 that long today, right.

21 MS. ELLIS: At this time we have  
22 six votes, so if every one can make sure that

1       they actually pushed the keypad, okay. We  
2       have all the votes with mean score of 1.375.

3               DR. GOODMAN: That sounds about  
4       like one point four to me okay? MS. ELLIS: And  
5       also what we need everyone to do is to state  
6       your score. Each individual person please.

7               DR. GOODMAN: Starting with Dr.  
8       Phurrough?

9               MS. ELLIS: Starting with Dr.  
10       Phurrough.

11              DR. GOODMAN: Let's get the scores  
12       out and then when we're done with the scores  
13       I'll ask for any other points to be made.

14              DR. PHURROUGH: I voted one.

15              DR. GOODMAN: We have to speak  
16       into the microphone because we have the  
17       background noise.

18              DR. PHURROUGH: I voted one.

19              MS. CABRAL-DANIELS: Rene Cabral-  
20       Daniels, one.

21              DR. HESELTINE: Peter Heseltine,  
22       two.

1 DR. JANOWITZ: Warren Janowitz,  
2 one.

3 DR. MCDONOUGH: Bob McDonough,  
4 one.

5 DR. SAADI: I actually voted  
6 three, but can I make a quick comment?

7 DR. GOODMAN: No, you can in a few  
8 minutes, we need every score first.

9 DR. SAADI: I might have done it  
10 wrong so that's why.

11 MR. SAMSON: David Samson, one.

12 DR. STEINBROOK: Robert  
13 Steinbrook, one.

14 DR. SEAL: Of course on paper,  
15 Brian Seal, one.

16 DR. RUDY: Also on paper, Yoram  
17 Rudy, one.

18 DR. GOODMAN: Dr. Saadi, sounds  
19 like you voted 3 so even if you reversed it  
20 you'd still be in the same place. What was  
21 your comment Dr. Saadi?

22 DR. SAADI: I did not understand,

1 I'm assuming that these patients did not have  
2 EKG or they had EKG?

3 DR. GOODMAN: They were defined as  
4 --

5 DR. SAADI: It's not a screening  
6 test.

7 DR. GOODMAN: I wish you had asked  
8 that before, which is what your responsibility  
9 was. Patients who are asymptomatic, patients  
10 at risk for the disease. Take it as you will.

11 DR. SAADI: Okay.

12 DR. GOODMAN: Okay. So it was  
13 1.374, was the score and that has implications  
14 for whether or not we're going to ask a  
15 subsequent question.

16 Let's now move to Question 1b,  
17 which is reliably and accurately detect  
18 coronary artery disease in patients with signs  
19 and symptoms suggestive of ACS with or without  
20 chest pain. And just to remind you and low to  
21 intermediate risk, was part of the definition.  
22 Dr. McDonough?

1 DR. MCDONOUGH: Just a quick  
2 clarification that second question. So the  
3 second question is whether it can detect, not  
4 whether it can detect better than anything  
5 else?

6 DR. GOODMAN: Correct, that was  
7 the gist of Dr. Steinbrook's question and  
8 clarification. There's no explicit comparator  
9 here. Thank you for that. Our TA people  
10 would you care to please provide your synopsis  
11 on 1b?

12 DR. COEYTAUX: Yes, we identified  
13 11 studies that were eligible for and  
14 pertinent to 1b. One of them compared one of  
15 the technologies to coronary angiography for  
16 the detection of coronary disease. And ten of  
17 them used biomarkers as the criteria and  
18 standard for detecting myocardial infarct, MI.

19 DR. GOODMAN: And did you want to  
20 tell us anything about the quality of those  
21 studies. Remember this was the adequacy of  
22 the evidence, not just counting studies.

1 DR. COEYTAUX: The largest trial  
2 that was conducted largely in the United  
3 States was the OCCULT trial, which was one of  
4 the ten that looked at the detection, the  
5 ability of the prime ECG to detect acute MI  
6 was a good quality study, followed the others  
7 with fair quality studies.

8 DR. GOODMAN: Sorry to keep  
9 pressing. A good quality study comprised what  
10 in this case?

11 DR. COEYTAUX: Good quality study  
12 would require a adequate criteria and  
13 standard. In this case we considered the  
14 study adjudicated diagnosis of acute MI as  
15 determined by the end of the hospital stay.

16 So that there was a panel of  
17 experts that determined that the diagnosis was  
18 correct. So that qualified as a good quality  
19 study.

20 That there was a minimum amount of  
21 bias, avoiding bias by not having test result  
22 of one test inform the interpretation of

1 another test.

2 And having adequate recording of  
3 the methods, the patient population and the  
4 outcomes. Those are three of the more  
5 important criteria that go into the quality  
6 rating.

7 DR. GOODMAN: Good, thank you very  
8 much.

9 DR. COEYTAUX: You're welcome.

10 DR. GOODMAN: Are there any on  
11 point specific comments from any of our  
12 speakers on the matter of 1b. Dr. Strobeck?

13 DR. STROBECK: Thank you. This  
14 question I think details the sweet spot of the  
15 MCG trials, not only my trial, but the three  
16 studies that were done that resulted in four  
17 publications between 2000 and 2005.

18 These people were at intermediate  
19 risk, they had some signs and symptoms, they  
20 were otherwise considered candidates for  
21 coronary angiography. And the performance of  
22 this technology was very good in this group of

1 people.

2 DR. GOODMAN: Never the less  
3 though, none of those studies was detected in  
4 the technology assessment. Though we  
5 acknowledge that the study was published a few  
6 weeks ago that might have been relevant,  
7 correct?

8 DR. STROBECK: The three studies  
9 that were done prior were excluded according  
10 to the discussion because they were felt to  
11 represent patients who were in the  
12 catheterizing laboratory experiencing a  
13 controlled amount of ischemia and the result  
14 was detected by MCG.

15 That was incorrect. These trials  
16 were done prior to the cath lab, they were  
17 done on patients that were referred for  
18 coronary angiography and therefore I think  
19 should be included.

20 DR. GOODMAN: Thank you for your  
21 point of view, Dr. Strobeck. Any comments on  
22 behalf of our panelists? Yes, Mr. Samson.

1                   MR. SAMSON: I think one of the  
2 points that the EPC raised was that by virtue  
3 of them be referred for coronary angiography  
4 they would be defined as high risk. Is that  
5 correct?

6                   DR. GOODMAN: And we do care about  
7 low and intermediate, not high.

8                   MR. SAMSON: Right and perhaps  
9 there was a mix of intermediate and high risk  
10 patients. But I would be curious if there  
11 were separate reporting of the results by risk  
12 category.

13                  DR. STROBECK: This is Dr.  
14 Strobeck. The protocol specified in all three  
15 of those studies, that patients that had acute  
16 coronary syndrome, were in the throes of an  
17 acute myocardial infarction or had ST  
18 elevation were absolutely excluded from the  
19 analysis.

20                  So those patients never were mixed  
21 in with the data. The only patients that were  
22 in that data set were patients that were

1 referred for coronary angiography. And on the  
2 day of the angiogram, they were totally  
3 stable, ready to undergo an elective  
4 procedure.

5 I can't see that those patients  
6 are considered high risk just because they're  
7 in a cath lab.

8 MR. SAMSON: My assumption is that  
9 the definition of risks are adhered to AHA  
10 guidelines, is that correct?

11 DR. GOODMAN: Dr. Strobeck, again.

12 DR. STROBECK: The AHA risk the  
13 Diamond Forrester scores and the Framingham  
14 scores all relate to a risk of a coronary  
15 event over a ten year period.

16 And intermediate risk goes  
17 anywhere from ten percent to 90 percent. So  
18 the patients and the incidents of coronary  
19 disease in the studies that we talked about  
20 was 41 percent, I think that's an intermediate  
21 risk.

22 DR. GOODMAN: Thank you. Dr.

1 Samson, are you satisfied at this point with  
2 this issue?

3 MR. SAMSON: Yes, it appears --

4 DR. GOODMAN: Okay. Let's have,  
5 Dr. Coeytaux, could you come in on that?  
6 Because we are, the matter at hand is  
7 exclusion versus inclusion fo certain studies.

8 DR. COEYTAUX: Yes, this is Dr.  
9 Coeytaux. Please correct me if I'm wrong, but  
10 at least one of the three studies that we had  
11 looked at and excluded stated specifically  
12 that all of the patients had known coronary  
13 artery disease.

14 In fact they had within six weeks.  
15 That's actually an important point, that we  
16 may be wrong, that I want to verify. We will  
17 take a moment to do that because my  
18 recollection from having read not long ago.

19 That at least one of the studies.  
20 They had, the patients had, known coronary  
21 artery disease and had been in the six within  
22 the six week period of having had a coronary

1 intervention.

2 So in our view these were patients  
3 with coronary artery disease and the closest  
4 classification given in the AHA guidelines is  
5 high risk, but they're with known risk. Known  
6 coronary artery disease, so that is the reason  
7 why we excluded them. That was my point.

8 DR. GOODMAN: Okay. Rather than  
9 kind of going back and forth on this does  
10 anyone have the study here?

11 DR. COEYTAUX: We do, and we'll  
12 get it in a moment.

13 DR. GOODMAN: Why don't you?

14 DR. COEYTAUX: Thank you.

15 DR. GOODMAN: It's worth taking a  
16 moment. If you could put your finger on that  
17 pretty soon that would be good. Go ahead, Mr.  
18 Samson.

19 MR. SAMSON: Assuming that this  
20 can get resolved, it appears to me that the --  
21 one of the key concerns here is the results of  
22 the meta analysis, in which there is

1 sensitivity, specificity, pooled estimates for  
2 both prime body surface mapping and standard  
3 ECG.

4 What the meta analysis shows is  
5 higher sensitivity and slightly lower  
6 specificity. The confidence intervals  
7 overlapped between the two modalities and  
8 there's a great deal of heterogeneity.

9 What I take away from that is that  
10 it's difficult to reach a conclusion with that  
11 much heterogeneity and with overlapping  
12 confidence intervals.

13 And I would suspect that part of  
14 the uncertainty about the results is the fact  
15 that this technology has been evolving. I'm  
16 curious if it's going to get to a point of  
17 maturity and that it could be studies in, you  
18 know, larger studies. It's not a content area  
19 where there's a shortage of study  
20 participants.

21 DR. GOODMAN: So you're looking at  
22 it not just at any particular study, you're

1 looking at the meta analysis of the available  
2 evidence. You're finding A, a lot  
3 heterogeneity and B, overlapping confidence  
4 intervals for the group of studies.

5 And you're also suggesting that  
6 the addition of any one more study might not  
7 kind of sway that entire body of findings of  
8 the meta analysis?

9 MR. SAMSON: Right, I would be  
10 very interested to see large studies.  
11 Comparative studies, perhaps not limited to  
12 diagnostic accuracy but also to health  
13 outcomes.

14 Even though this particular  
15 question really deals with diagnostic  
16 accuracy.

17 DR. GOODMAN: Good, thanks. That  
18 something of which you may want to remind us  
19 when we look at evidence gaps later on. But  
20 thank you for raising it now, it is relevant  
21 to this question. Dr. Coeytaux, have you had  
22 a chance to take a look at that?

1 DR. COEYTAUX: Yes.

2 DR. GOODMAN: Anything you would  
3 like to report?

4 DR. COEYTAUX: I would, please.  
5 So we are talking about three studies all of  
6 which are unique studies. So they aren't  
7 exactly the same on populations.

8 DR. GOODMAN: Please speak right  
9 into the microphone for the panel to hear.

10 DR. COEYTAUX: Yes. So one study  
11 published in 2008 by Dr. Grube, the patient  
12 population, and I'll quote from the study.

13 "These patients represented a  
14 convenient sample in that each patient was  
15 already scheduled for coronary angiography for  
16 any indication. And had undergone at least  
17 one coronary vascularization procedure. At  
18 least six weeks before the scheduled  
19 angiography."

20 So they had already undergone a  
21 procedure.

22 DR. GOODMAN: That was an and not

1 an or?

2 DR. COEYTAUX: That's an and. Now  
3 there is one, another study here that excluded  
4 patients had had a previous vascularization.

5 But then another reason why we  
6 consider this group to be representative of a  
7 largely high risk is because they mentioned  
8 the number of patients who had a known history  
9 of myocardial infarction.

10 So the second study, also by Dr.  
11 Grube, published in 2007, of 562 patients, who  
12 were scheduled for coronary angiography, 44  
13 patients, looks like about maybe 8 percent.  
14 And I'm doing that in my head.

15 Had a history of myocardial  
16 infarction more than six weeks prior to  
17 angiography. And no patients presented with  
18 acute coronary syndrome at the time of the  
19 study.

20 So the first one that I just  
21 mentioned we clearly would have excluded  
22 because they had a known diagnosis of coronary

1 artery disease. Well, actually that's not  
2 necessarily true. They had had previous  
3 vascular coronary interventions. And  
4 therefore high risk in our view.

5 And then the other one there was a  
6 proportion of patients who had known MI and  
7 also were excluded if they had acute coronary  
8 syndrome.

9 So we struggled with these  
10 studies, we had included them in the first  
11 report and we wanted to make use of this  
12 important information.

13 But no matter how we looked at it  
14 we concluded that for the purpose of this,  
15 these key questions, that these patients did  
16 not in our view represent the patients that  
17 are under consideration now with Question 1b,  
18 in our view.

19 DR. GOODMAN: Okay. Thank you,  
20 Dr. Coeytaux. Mr. Samson, does this sound in  
21 line with what you were thinking?

22 MR. SAMSON: Well, this gets at

1 the issue of the size of the body of evidence.  
2 And so according to BPC, they're not  
3 interested in expanding it.

4 DR. GOODMAN: Okay. Let's proceed  
5 to vote then. Does anybody have any very  
6 important information that is directly  
7 relevant to this question that we have not  
8 considered? Directly relevant on this point?

9 All right. Let's proceed to vote  
10 then. This is Question 1b. And we're looking  
11 at adequacy of evidence again, correct?

12 How confident are you that there's  
13 adequate evidence to determine whether or not  
14 SAECG technologies, any of them, are able to  
15 reliable and accurately detect B, coronary  
16 artery disease in patients with signs and  
17 symptoms suggestive of ACS with or without  
18 chest pain and low to intermediate risk.

19 One is low confidence, five is  
20 high confidence, three is intermediate.

21 MS. ELLIS: We have six of eight.

22 DR. GOODMAN: All right. I see

1       what, 2.625. Thank you. All right. So those  
2       are Questions 1a and b. Based on those  
3       findings and with our kind of rule about  
4       exceeding a mean vote of two and a half.  
5       We'll dispense with Question 2a. But we'll  
6       pursue Question 2b. We'll pursue Question  
7       2b.

8                       Were there any comments before we  
9       proceed? Dr. Steinbrook?

10                      DR. STEINBROOK: Is there a vote?

11                      MS. ELLIS: Yes.

12                      DR. GOODMAN: Thank you for  
13       reminding me. Dr. Phurrough?

14                      DR. PHURROUGH: Steve Phurrough,  
15       three.

16                      MS. CABRAL-DANIELS: Rene Cabral-  
17       Daniels, one.

18                      DR. HESELTINE: Peter Heseltine,  
19       three.

20                      DR. JANOWITZ: Warren Janowitz,  
21       three.

22                      DR. MCDONOUGH: Bob McDonough,

1 four.

2 DR. SAADI: Ryan Saadi, three.

3 MR. SAMSON: David Samson, one.

4 DR. STEINBROOK: Robert

5 Steinbrook, three.

6 DR. SEAL: Brian Seal, three.

7 DR. RUDY: Yoram Rudy, three.

8 MS. ELLIS: Thank you.

9 DR. GOODMAN: Thank you. Any  
10 final comments before we proceed? Any  
11 explanation you want at all for a point for  
12 the agency to recall when it revisits this?  
13 Okay. Seeing none.

14 All right. We're going to proceed  
15 now to Question 2b, having skipped 2a. Now  
16 rather than the adequacy of evidence, we're  
17 going to talk about what the evidence tells  
18 us.

19 And so the wording in Question 2b  
20 is as follows. If the result of Question 1 is  
21 at least intermediate, which it is for  
22 Question b, in any of the conditions noted,

1 again that's B, how confident are you that ECG  
2 based signal analysis technologies are able to  
3 reliably and accurately detect, B, coronary  
4 artery disease in patients with signs and  
5 symptoms suggestive of ACS with or without  
6 chest pain. In low to intermediate risk.

7 And again, as we established  
8 earlier, we're not looking at a particular  
9 comparator. So if I can call the gentleman  
10 from the EPC up once again. If you would  
11 address briefly your findings and indicates  
12 for 2b?

13 DR. COEYTAUX: This is Remy  
14 Coeytaux, we found 11 studies that evaluated  
15 the performance of two devices. All of the  
16 patients that were equated in these studies  
17 fit under the category of patients with signs  
18 and symptoms suggestive of ACS with or without  
19 chest pain.

20 The results, I believe you're  
21 looking for results?

22 DR. GOODMAN: Yes.

1 DR. COEYTAUX: So the results are  
2 that there was, one of the devices is the LP  
3 3000 system, a signal averaging device. And  
4 there was not a statistical significant  
5 improvement. But it's not a comparator.

6 There was sensitivity of 68  
7 percent, I'm sorry I don't have that on top of  
8 my head. There is evidence of sensitivity for  
9 this device compared to coronary  
10 catheterization for the diagnosis of coronary  
11 artery disease.

12 And then there are another ten  
13 studies that evaluated the prime ECG to detect  
14 myocardial infarction. And a meta analysis  
15 with a fair degree of, large degree of  
16 heterogeneity came up with an estimate, a  
17 point estimate for both the sensitivity and  
18 the specificity of the prime EKG.

19 And I'm afraid I don't know those  
20 numbers off the top of my head.

21 DR. GOODMAN: Mr. Leisy has  
22 something.

1 DR. COEYTAUX: Yes, thank you.

2 I'll come prepared with a report next time I'm  
3 up here. The meta analysis of eight of the  
4 ten studies and they did not explain why two  
5 are excluded. They were excluded, because one  
6 was a very small sample size and seemed to  
7 have changed the result in a way that did not  
8 appear to be representative.

9 And another one, clearly was a  
10 very early study that explicitly used a  
11 different algorithm for the prime ECG. And so  
12 we excluded that study as well. Although we  
13 also did an overall meta analysis that had  
14 very similar results.

15 But we felt the more robust meta  
16 analysis, the in the report that included  
17 eight studies, and they found that the  
18 sensitivity of the prime ECG for the diagnosis  
19 of acute myocardial infarction was 71 percent,  
20 95 percent confidence interval of 46 to 88.

21 And that the specificity was 90  
22 percent with a 95 percent confidence interval

1 of ranging from 83 to 94.

2 DR. GOODMAN: In the case of the  
3 first, the LP3000, that was where there was  
4 one study? What did you say about the  
5 confidence interval?

6 DR. COEYTAUX: I didn't mention  
7 the confidence interval. We don't have it on  
8 our slides, I can take a moment to find it  
9 here.

10 What I know is it is not  
11 statistically significantly different from the  
12 ECG. But I think right now we're not looking  
13 at a comparator. I will try to find an  
14 answer, would you like the confidence interval  
15 around that?

16 DR. GOODMAN: I thought you had  
17 said earlier it was broad.

18 DR. COEYTAUX: I didn't have it in  
19 my presentation and I don't have it in my head  
20 what the confidence interval for that study  
21 is. We didn't present that.

22 DR. GOODMAN: All right. I'm

1       sorry.

2                   DR. COEYTAUX:  I'm sorry we didn't  
3       have the, I imagine it's in here, and I can  
4       find it if you like.

5                   DR. GOODMAN:  The particular  
6       finding that you reported though was versus  
7       something was not statistically significant?

8                   DR. COEYTAUX:  Yes, so the study  
9       was designed to estimate the sensitivity and  
10      specificity of the index test.  The LP3000  
11      with coronary catheterization as the gold  
12      standard.

13                   They also did the same for the EKG  
14      and our comment was that there was a higher  
15      estimate for the sensitivity of the test  
16      device, but that was not statistically  
17      significantly greater than the point estimate  
18      for the EKG.

19                   But the sensitivities were the  
20      same for both those tests.

21                   DR. GOODMAN:  Good, thank you very  
22      much.

1 DR. COEYTAUX: The specificity was  
2 the same.

3 DR. GOODMAN: The specificity.  
4 Okay. Any questions or comments on the part  
5 of the panel for 2b? For 2b, this is what the  
6 evidence is saying about the findings. Does  
7 any speaker have any on point issue to raise  
8 with this question? Okay. We're going to get  
9 a clarification from Dr. Coeytaux.

10 DR. COEYTAUX: I very much  
11 apologize. I now have the report in front of  
12 me this is referring to the single study of  
13 the LP3000 signal averaging system.

14 And I significantly misspoke. I'm  
15 going to read from the report here. "The  
16 improved sensitivity of signal averaging ECG  
17 relative to the 12-lead ECG was statistically  
18 significant at the P level of .01.

19 DR. GOODMAN: Okay.

20 DR. COEYTAUX: So that is in  
21 contradiction to what I previously said.

22 DR. GOODMAN: Good, the record is

1 corrected, thank you very much. I'm glad that  
2 you stayed on top of that. Yes, Dr. Imhoff?  
3 This is Dr. Imhoff.

4 DR. IMHOFF: I would like to make  
5 a general comment on this process.

6 DR. GOODMAN: Dr. Imhoff, I hope  
7 your general comment has something at least  
8 vaguely to do with this question.

9 DR. IMHOFF: With this question  
10 and the previous question.

11 DR. GOODMAN: Go right ahead.

12 DR. IMHOFF: I'm slightly  
13 concerned as a scientist and as a researcher  
14 and also statistician that you're basing your  
15 vote on incomplete evidence. As we already  
16 had some unresolved discussions points with  
17 the TA report.

18 My impression is that the TA  
19 report is the major basis of your voting  
20 process and I doubt the scientific validity of  
21 that process. A little bit concerned. That's  
22 the only comment I want to make.

1 DR. GOODMAN: Thank you Dr.  
2 Imhoff, if you or anybody else has a  
3 particular reason to disagree with the TA we'd  
4 be glad to hear it briefly today, or in  
5 writing later on. Thus far I've heard none.

6 And so far as for particular  
7 reason, if there's particular thing that you  
8 thought was done inappropriately we'd like to  
9 hear it. We pursued the matters of  
10 definitions of these terms a few times.

11 We pursued the matter of a study  
12 that was published a few weeks ago with regard  
13 with what we could conclude or not conclude  
14 from it. Which I think is quite generous on  
15 the part of the process.

16 So your point is heard, I don't  
17 know that you can back it up at this point  
18 just yet however. So, Dr. Shen?

19 DR. SHEN: The largest studies  
20 that were conducted.

21 DR. GOODMAN: Into the microphone,  
22 please.

1 DR. SHEN: The three major studies  
2 that were conducted actually the focus was on  
3 people who have intermediate risks.

4 Unfortunately there were patients with  
5 myocardial infarct which was about 8 percent  
6 for the large size study, about 500 patients.

7 And that, if we excluded those  
8 patients with the myocardial infarct, 8  
9 percent of the study the sensitivity and  
10 specificity don't change.

11 So if you look at largely that the  
12 study that was conducted, in general under Dr.  
13 Grube and also the Hosokawa on this study were  
14 conducted in Asia.

15 And all of these studies of  
16 patients as well as the patients that we  
17 studied in North America, they are all  
18 considered intermediate. We look at risk  
19 factors or look at the post pretest of  
20 probability and your graphic data, so about 41  
21 percent.

22 DR. GOODMAN: Thank you, Dr. Shen,

1 we did read directly from the published  
2 reports with regard to who was included and  
3 who wasn't. So what the study said is a  
4 matter of record.

5 Any further comments or questions  
6 on 2b, from panelists? From any of our  
7 speakers, anything in particular on 2b you'd  
8 like to add? No, okay. Yes, Dr. Seal.

9 DR. SEAL: They said there were  
10 three studies, I heard two, was there a third  
11 study as well? What was the other study that  
12 you mentioned?

13 DR. GOODMAN: Dr. Shen, if you  
14 have an answer you've got to approach the  
15 microphone.

16 DR. SHEN: Yes, one study was  
17 conducted in Westchester County Medical Center  
18 under Dr. Weiss. The largest study was in  
19 Germany under Dr. Grube, and then more  
20 intensive study conducted in Asia. Which was  
21 also a pretty sizable study.

22 DR. GOODMAN: Thank you. Any

1 further comments? Okay. 2b, let's vote on  
2 that. How confident are you that ECG based  
3 signal analysis technologies, could be at  
4 least one, are able to reliably and accurately  
5 detect coronary artery disease in patients  
6 with signs or symptoms suggestive of ACS with  
7 or without chest pain in low to intermediate  
8 risk.

9 One, low confidence, three  
10 intermediate confidence, five high confidence.  
11 Please press your buttons.

12 MS. ELLIS: All the votes are in.

13 DR. GOODMAN: Okay. Is that a  
14 2.626

15 MS. ELLIS: 2.625.

16 DR. GOODMAN: Thank you very much.  
17 Any further comments before we go to the next  
18 question. Dr. Phurrough. Oh we need to hear  
19 all the votes, yes. Dr. Phurrough.

20 DR. PHURROUGH: Steve Phurrough,  
21 two.

22 MS. CABRAL-DANIELS: Rene

1 Cabral-Daniels, three.

2 DR. HESELTINE: Peter Heseltine,  
3 four.

4 DR. JANOWITZ: Warren Janowitz,  
5 three.

6 DR. MCDONOUGH: Bob McDonough,  
7 two.

8 DR. SAADI: Ryan Saadi, three.

9 MR. SAMSON: David Samson, two.

10 DR. STEINBROOK: Bob Steinbrook,  
11 two.

12 DR. SEAL: Brian Seal, three.

13 DR. RUDY: Yoram Rudy, three.

14 DR. GOODMAN: Okay. All those  
15 have been recorded?

16 MS. ELLIS: Yes.

17 DR. GOODMAN: Thank you, Ms.

18 Ellis. All right. Let's proceed now to  
19 Question 3. And once again because we didn't  
20 address in question 2a because we had a low  
21 score in 1a. Then if I'm not mistaken we will  
22 not address 3a in this instance but we will

1 address 3b. I believe that's correct, Dr.  
2 Rollins, right?

3 DR. ROLLINS: Right.

4 DR. GOODMAN: So we're not going  
5 to do 3a, we're going to address 3b here.  
6 This is another matter of adequacy of  
7 evidence.

8 And in four we'll get to what the  
9 evidence might say. If we could have our  
10 technology assessment duo provide a synopsis  
11 of what pertains to 3b, what evidence pertains  
12 to 3b.

13 This is improves decision making.  
14 And I'll say it again. How confident are you  
15 that there is adequate evidence to determine  
16 whether or not the incremental information,  
17 incremental information, obtained from SAEKG  
18 technologies beyond that provided by the  
19 standard 12-lead ECG, improves physician  
20 decision making in the management of coronary  
21 artery disease in patients with signs and  
22 symptoms suggestive of ACS with or without

1 chest pain.

2 DR. COEYTAUX: This is Remy  
3 Coeytaux, we did not find any studies that met  
4 our inclusion criteria that were designed to  
5 answer this question or really did provide a  
6 clear evidence in support of the question  
7 about providing -- having an effect on  
8 physician decision making.

9 DR. GOODMAN: Okay. Thank you.  
10 Any of our speakers have anything of substance  
11 to add to this particular question? Yes, Dr.  
12 Strobeck.

13 DR. STROBECK: Yes, thank you.  
14 I'm just curious for my own edification, what  
15 is the bar, where is the bar set for a  
16 diagnostic test that's probably twice as  
17 accurate as SPECT MPI, at detecting coronary  
18 disease.

19 When you have a very accurate test  
20 that way, what other evidentiary information  
21 do you need to show that it would affect  
22 physician behavior?

1                   It seems intuitive that a  
2           physician is going to gravitate towards the  
3           most accurate diagnostic tests.

4                   DR. GOODMAN: Yes, thank you for  
5           your question Dr. Strobeck. In fact intuition  
6           often does not play out in practice, as I'm  
7           sure you know.

8                   There are many tests that are  
9           highly sensitive specific positive/negative  
10          predictive value. They may be blood tests,  
11          they may be imaging, genetic tests, what have  
12          you.

13                  And the presents of even highly  
14          accurate information is often not found to  
15          affect a clinician's decision. So what we're  
16          looking for here, and this is documented CMS  
17          documentation by the coverage analysis group.

18                  You'll find it documented in  
19          evidence appraisal guidelines by the major  
20          medical professional societies. That we're  
21          looking for some evidence, not intuition, that  
22          somebody's mind was changed by the

1 availability of this information on a test.

2           So its got to go beyond it's  
3 obvious, has somebody actually followed a  
4 group of physicians in making a decision or  
5 could infer sometimes from changes in  
6 utilization. That would appear to be a  
7 causal arising from having had a test in  
8 particular.

9           I appreciate your asking the  
10 question. Any further comments on the part of  
11 our panel or anyone else?

12           By the way, while our panel is  
13 thinking about how it's going to vote here,  
14 I'll just add for Dr. Strobeck and others.  
15 One of these to look for in the literature.

16           It's sometimes called an  
17 analytical frameworks, or causal pathways that  
18 lay out left to right. A population at risk  
19 on the left side of the page and at the far  
20 right side of the page is a box that will say  
21 treatment decision.

22           And further to the right of that

1 is outcome. And along the way we want to see  
2 that steps that get you from a test a result  
3 to a decision to change in outcome. So those  
4 are part of the standard analytical  
5 frameworks.

6 Okay. I see no hands raised for  
7 3b, so let's go ahead and answer Question 3b  
8 again, this is an adequacy question. How  
9 confident are you that there is adequate  
10 evidence to determine whether or not the  
11 incremental information obtained from SAEKG  
12 technologies beyond that provided by the  
13 standard 12-lead ECG.

14 So we've got a comparator here.  
15 Looking for marginal difference I should say.  
16 Improves physician decision making in the  
17 management of coronary artery disease in  
18 patients with signs/symptoms suggestive of ACS  
19 with or without chest pain.

20 And please do vote. One's low,  
21 three is intermediate, five is high. And  
22 again I apologize for rereading the question.

1 We want to do that for the record and just to  
2 remind everybody where we are.

3 MS. ELLIS: 1.125.

4 DR. GOODMAN: Okay. So all votes  
5 are in, and Ms. Ellis reports that is 1.125.  
6 I don't know that we need all the significant  
7 figures but that's what the map says, so thank  
8 you. 1.125 that would not meet the threshold  
9 of 2.5 which would take us to the next  
10 question. But let's get everybody's vote  
11 verbally, Dr. Phurrough.

12 DR. PHURROUGH: Steve Phurrough,  
13 one.

14 MS. CABRAL-DANIELS: Rene  
15 Cabral-Daniels, one.

16 DR. HESELTINE: Peter Heseltine,  
17 one.

18 DR. JANOWITZ: Warren Janowitz,  
19 two.

20 DR. MCDONOUGH: Bob McDonough,  
21 one.

22 DR. SAADI: Ryan Saadi, one.

1 MR. SAMSON: David Samson, one.

2 DR. STEINBROOK: Robert

3 Steinbrook, one.

4 DR. SEAL: Brian Seal, two.

5 DR. RUDY: Yoram Rudy, one.

6 DR. GOODMAN: Thank you very much.

7 Given the mean score here, we won't pursue

8 Question 4 is that correct, Dr. Rollins?

9 DR. ROLLINS: Right, yes.

10 DR. GOODMAN: Okay, we won't do

11 that then. Does anybody want to make any

12 comments, any panelists want to make any

13 comments about our findings for Question 3 at

14 all? Before we proceed I just want to make

15 sure we've got this covered.

16 All right. Then let's proceed to

17 Question 5. Five and six are paired as have

18 been our previous two pairs here. This has to

19 do with adequacy of evidence. This is with

20 regard to that incremental information

21 obtained from the SAEKG technologies that once

22 again, beyond the standard 12-lead ECG.

1                   But this time we're talking about  
2                   eliminating the need for at the level of an  
3                   individual patient, not across the population.  
4                   Can eliminate the need for any of those four  
5                   following technologies.

6                   And Dr. Rollins and Dr. Miller, I  
7                   guess we want to look at these individually do  
8                   we? Or any? Dr. Phurrough? Individually?

9                   DR. PHURROUGH: I think, because  
10                  they're going to be different, they could be  
11                  different.

12                  DR. GOODMAN: Okay. So of the  
13                  three, yes, A, B, and C. So we're going to  
14                  need to do respond to all three of these. Our  
15                  TA team, would you care to come to the  
16                  microphone and tell us what you can about your  
17                  findings for these.

18                  DR. COEYTAUX: Would you like me  
19                  to summerize for all three? Or one at a time?  
20                  How would you like me to do that?

21                  DR. GOODMAN: Let's do one at a  
22                  time. Let's just kind of keep our train of

1       thought together here. I know that's going to  
2       take a lot of standing up and down, but please  
3       proceed.

4                   DR. COEYTAUX: That's fine, very  
5       good. So this is about adequacy of  
6       information, for 5a, diagnostic laboratory  
7       testing. We identified 11 studies that looked  
8       at the devices, ten of those studies,  
9       incorporated the use of biomarkers for as a  
10      criterion standard for the diagnosis of MI.

11                   One of these studies was a good  
12      quality study. Which was the large OCCULT  
13      study. And the outcome of that study was to  
14      determine whether or not there was a acute  
15      myocardial infarction that included  
16      biomarkers.

17                   But they also included additional  
18      information that was obtained over the course  
19      of the hospitalization.

20                   But the other studies in that's  
21      done with the prime ECG used biomarkers, CK,  
22      MB levels specifically as the criterion

1 standard. And those were all fair quality  
2 studies.

3 DR. GOODMAN: Fair, and what's  
4 above and below fair?

5 DR. COEYTAUX: There are three  
6 quality ratings. There's poor, fair and good.  
7 And poor is, we would rate a quality poor if  
8 there is evidence of, a high likelihood of  
9 bias being introduced for a number of reasons.

10 Or very poor reporting so that we  
11 couldn't assess the degree of bias. None of  
12 the studies were rated as poor.

13 Fair quality studies are ones that  
14 have a moderate risk of bias. In the design  
15 and the conduct of the study, or the reporting  
16 may not be quite sufficient enough to give us  
17 confidence that there isn't such bias. And  
18 that was on most of the studies.

19 The main reason for rating a  
20 quality poor was the incomplete criterion  
21 standard, in this case, which was the very  
22 question we looking at. Which was the

1       biomarkers which we considered not a complete,  
2       fully adequate criterion standard, and  
3       therefore just that would bring the quality  
4       down from good to poor.

5               DR. GOODMAN:  Thank you.  Again  
6       we're going to have to do these one at a time.  
7       Panel, any question about A,  diagnostic  
8       laboratory testing, for example troponin?  Dr.  
9       Steinbrook.

10              DR. STEINBROOK:  It's really a  
11       comment about the common wordage under five.  
12       That we're presupposing incremental  
13       information obtained from the SAEKG technology  
14       beyond that provided by the standard ECG.

15              And then we go on to A, B, and C.  
16       But the way I look at this is that for the one  
17       device that had most of the studies my  
18       recollection is that the confidence intervals  
19       for the difference in the sensitivity between  
20       ECG and SAEKG overlapped.

21              And then you have one study, one  
22       study of the other device, the LP3000 and

1 while in that situation the LP3000 was more  
2 sensitive than the ECG with the P, less than  
3 .01. If you actually go back and look at the  
4 numbers it one study and you've got a universe  
5 of 108 and it's 75 versus 60 which is driving  
6 the .01.

7 So those numbers are the numbers  
8 and that's it. There's no other evidence  
9 beyond that. So I'm just talking about the  
10 first part of this before we get into A, B and  
11 C.

12 DR. GOODMAN: Okay. So do you  
13 propose that we look at it any differently or  
14 just?

15 DR. STEINBROOK: No, but I think  
16 the common part five, at least the way I  
17 approached this, drive some of my thinking  
18 before I even get to these other things down  
19 below.

20 DR. GOODMAN: Okay. Comments by  
21 any of the other panelists on interpreting  
22 this? I think we've got to take it literally

1 unless somebody pushes us off that definition.  
2 Okay. Any comments from one of our speakers,  
3 on the matter of diagnostic laboratory  
4 testing. Yes, this is Dr. Beker.

5 DR. BEKER: This is actually a  
6 question about the wording of Question Number  
7 5 and the wording "eliminate the need" at the  
8 level of an individual patient.

9 I just wanted to ask the authors  
10 of these questions whether the intention was  
11 actually, eliminate the need is quite an  
12 extreme term. So was the intention, reduce  
13 the need, we know that some of the  
14 technologies reduce unnecessary further  
15 procedures.

16 DR. GOODMAN: Dr. Miller is  
17 approaching the microphone.

18 DR. MILLER: I think that you  
19 could perhaps say it would, that the SAECG  
20 technology would substitute for, so yes, we  
21 are talking about totally eliminating the  
22 test, either A, B, or C.

1 DR. GOODMAN: There would be no  
2 need for, given this incremental information  
3 if it is available?

4 DR. MILLER: Yes, correct.

5 DR. GOODMAN: Okay. That was the  
6 intention, thank you.

7 DR. PHURROUGH: For an individual  
8 patient, right?

9 DR. MILLER: Yes.

10 DR. GOODMAN: Right. And that's  
11 an important point, and it's explicit in the  
12 question this is not a population, cross  
13 population, finding. Dr. Rollins?

14 DR. ROLLINS: I'd just like to  
15 make a quick comment. When we posed, A,  
16 diagnostic laboratory testing, troponin. We  
17 were making the assumption that this test  
18 could detect myocardial ischemia.

19 Based on this mornings  
20 conversation it was pointed out that  
21 myocardial necrosis was made from troponin  
22 diagnosis.

1 DR. MILLER: To clarify what we  
2 were thinking, the difference between unstable  
3 angina and a NSTEMI is whether or not you have  
4 a positive biomarker or positive troponin. So  
5 that was the thought process behind this  
6 question. That instead of using a biomarker  
7 to make that distinction, that you could use  
8 an SAECG technology.

9 DR. GOODMAN: Thank you both.  
10 Okay. Further points to be made with regard  
11 to diagnostical laboratory testing for example  
12 troponin, in this one?

13 Okay. Let's call the question  
14 again, this is an adequacy of evidence  
15 question now, and adequacy of evidence  
16 question.

17 How confident are you that there  
18 is adequate evidence to determine whether or  
19 not the incremental information obtained from  
20 SAECG technologies, beyond that provided by  
21 the standard 12-lead ECG, can eliminate the  
22 need.

1                   And you heard what that meant, at  
2                   the level of an individual patient, you heard  
3                   that was well. For diagnostic laboratory  
4                   testing of for example, troponin. Scale of  
5                   one to five, one low confidence, three  
6                   intermediate, five, high. Adequacy of  
7                   evidence.

8                   There it is, I see a vote of 1.5  
9                   as a mean. Dr. Phurrough, your score?

10                  DR. PHURROUGH: Steve Phurrough,  
11                  four.

12                  MS. CABRAL-DANIELS: Rene  
13                  Cabral-Daniels, two.

14                  DR. HESELTINE: Peter Heseltine,  
15                  one.

16                  DR. JANOWITZ: Warren Janowitz,  
17                  one.

18                  DR. MCDONOUGH: Bob McDonough,  
19                  one.

20                  DR. SAADI: Ryan Saadi, one.

21                  MR. SAMSON: David Samson, one.

22                  DR. STEINBROOK: Robert

1 Steinbrook, one.

2 DR. SEAL: Brian Seal, one.

3 DR. RUDY: Yoram Rudy, one.

4 DR. GOODMAN: Thank you all. 1.5,  
5 that will mean that we won't pursue this  
6 matter in the subsequent question in what the  
7 evidence tells us.

8 Lets proceed to 5b. The question  
9 is the same. This time it's with regard to  
10 the need for noninvasive tests, noninvasive  
11 tests of cardiac anatomy functioning, example,  
12 stress testing, echocardiography.

13 These are noninvasive tests, we'll  
14 get to invasive next. Yes, Dr. Coeytaux on  
15 this matter of noninvasive testing?

16 DR. COEYTAUX: We did not find any  
17 included studies, eligible studies that  
18 address this question.

19 DR. GOODMAN: No studies. Thank  
20 you. Do our speakers have anything to suggest  
21 or assert on this? Dr. Strobeck, yes, sir?

22 DR. STROBECK: I would only ask

1 the panel to consider the trial that we  
2 presented today. Which was the noninvasive  
3 comparison of SA technology to SPECT MPI and  
4 showed that the SA technology did very well.

5 DR. GOODMAN: Okay. Thank you,  
6 and this was the October 2011 study, it was  
7 too recent to be entered here?

8 DR. STROBECK: That's correct.

9 DR. GOODMAN: Thank you for  
10 raising that. Any questions on the part of  
11 our panel? Panel we can only deal with the  
12 evidence that's in front us but again I can't  
13 tell you to not regard anything else you might  
14 have heard. That's quite fine, that's up to  
15 you.

16 All right. Would you please vote  
17 then on a scale of one to five, with regard to  
18 these noninvasive tests. This is an adequacy  
19 of evidence issue, incremental information  
20 eliminate the need for noninvasive tests.

21 The score is posted, it is 1.25,  
22 Dr. Phurrough, your score?

1 DR. PHURROUGH: Steve Phurrough,  
2 two.

3 MS. CABRAL-DANIELS: Rene  
4 Cabral-Daniels, one.

5 DR. HESELTINE: Peter Heseltine,  
6 two.

7 DR. JANOWITZ: Warren Janowitz,  
8 one.

9 DR. MCDONOUGH: Bob McDonough,  
10 one.

11 DR. SAADI: Ryan Saadi, one.

12 MR. SAMSON: David Samson, one.

13 DR. STEINBROOK: Robert  
14 Steinbrook, one.

15 DR. SEAL: Brian Seal, two.

16 DR. RUDY: Yoram Rudy, one.

17 DR. GOODMAN: Thank you all. Any  
18 closing comments on that one? No, then let's  
19 proceed to 5c, same question but the matter  
20 this time with regard to eliminating the need  
21 is invasive tests, invasive test of cardiac  
22 anatomy or functioning, for example, coronary

1 angiography.

2 And again this is an adequacy of  
3 evidence question, incremental information  
4 obtained from the SAECG beyond that provided  
5 by the standard 12-lead ECG, eliminating need  
6 at the level of individual patient for  
7 invasive tests of cardiac anatomy for  
8 functioning.

9 Please do vote. Enter your vote.  
10 Got three more coming. All votes are in, I  
11 see 1.375. Dr. Phurrough, your vote?

12 DR. PHURROUGH: Steve  
13 Phurrough, four.

14 MS. CABRAL-DANIELS: Rene  
15 Cabral-Daniels, one.

16 DR. HESELTINE: Peter Heseltine,  
17 one.

18 DR. JANOWITZ: Warren Janowitz,  
19 one.

20 DR. MCDONOUGH: Bob McDonough,  
21 one.

22 DR. SAADI: Ryan Saadi, one.

1 MR. SAMSON: David Samson, one.

2 DR. STEINBROOK: Robert

3 Steinbrook, one.

4 DR. SEAL: Brian Seal, two.

5 DR. RUDY: Yoram Rudy, two.

6 DR. GOODMAN: Thank you all. Any  
7 explanatory or closing comments on this issue?  
8 Dr. Phurrough.

9 DR. PHURROUGH: Since I was a  
10 significant outlier on A and C I thought that  
11 I would explain. I think there is sufficient  
12 information for us to recognize that these  
13 technologies are not intended to replace  
14 either a diagnostic test for an MRI, the  
15 troponins or angiography.

16 I think we have enough information  
17 to recognize that they're not intended to  
18 replace that. We don't have enough  
19 information to determine whether they should  
20 replace some of these other noninvasive tests.  
21 So that's that's why I voted four, I think we  
22 can make the determination, they are not

1 intended to replace those.

2 DR. GOODMAN: Good, thanks for  
3 that clarification, very helpful and I think  
4 the agency will find that enlightening. Thank  
5 you. Yes, Dr. Strobeck. I find your comments  
6 usually enlightening, Dr. Phurrough.

7 DR. STROBECK: Yes, and I totally  
8 agree with Dr. Phurrough, these technologies,  
9 I think can replace or at least change the  
10 decision to do an invasive test on a patient  
11 by patient basis.

12 Not across the board, it's not  
13 going to replace coronary angiography. But on  
14 a given patient with a low score, that patient  
15 may not need an angiogram. It's going to save  
16 a lot of unnecessary angiograms.

17 DR. GOODMAN: Good, thank you, Dr.  
18 Strobeck, your point is well taken.

19 All right. Then we would proceed  
20 to Question 6, however the criterion for  
21 pursuing Question 6 involves the average score  
22 of the parts of five A, B, and C, none of

1 which achieved the threshold of 2.5.

2 Therefore we'll need to proceed to the next  
3 question. Any other comments before we start  
4 Question 7, which deals with patient outcomes.  
5 Any comment on five or six, in addition to Dr.  
6 Phurrough's? Dr. Saadi, yes? Directly into  
7 the microphone.

8 DR. SAADI: Will you clarify the  
9 definition of outcomes for all of us?

10 DR. GOODMAN: I'd be glad to. And  
11 all I have to do is read what's on front of  
12 me. On the first page of the preamble is  
13 Paragraph 4, and it says health outcomes of  
14 greatest interest.

15 Health outcomes of greatest  
16 interest include mortality, MI, that's  
17 myocardial infarction, cardiac function and  
18 quality of life. Those are health outcomes.

19 If I might add health outcomes  
20 typically do not include biomarkers or what  
21 are often called intermediate end points.  
22 These are things that happen to patients,

1 things that patients can feel usually.

2 Mortality, Myocardial infarction, cardiac  
3 function and quality of life.

4 I will add just for the record,  
5 Dr. Saadi, that in some cases certain  
6 biomarkers have been validated repeatedly as  
7 being highly associated with or highly  
8 predictive of health outcomes such as these.

9 And of those instances one might  
10 therefore use such a surrogate. So it is  
11 possible that some biomarkers do indeed  
12 substitute very well for health outcome.

13 It's your judgement to decide  
14 whether or not that applies in this case. But  
15 just clarifies the definition. Thank you.

16 Okay. If we could have Dr.  
17 Coeytaux approach the mic as we're going to  
18 lay out Question 7. This has to do with  
19 adequacy of evidence again, not what evidence  
20 says, adequacy of evidence regarding whether  
21 or not the use of SAECG technologies  
22 significantly improves patient health

1 outcomes.

2 So points of clarification, SAECC  
3 technologies doesn't have to be all of them,  
4 will take any of them. Not just improve  
5 patient health outcomes as defined a moment  
6 ago, but significantly improves them. Would  
7 you care to comment on Question 7, Dr.  
8 Coeytaux?

9 DR. COEYTAUX: Yes, in our report  
10 we state that there were two studies that  
11 provided some information that may relate to  
12 this question. One of the studies did not  
13 actually publish or report the data. So about  
14 outcomes so it really isn't helpful to this  
15 question.

16 The other study is a good quality  
17 study, it's this OCCULT trial that looked at  
18 the prime ECG. However it was not designed to  
19 answer this specific question. It is not  
20 designed to answer this specific question.

21 But at the very end of the results  
22 section they do comment that there were

1 differences in outcomes in terms of mortality  
2 based on the findings of the prime EKG  
3 compared to the findings of the standard ECG.

4 And if you'd like me to tell you  
5 those. It was an incidental finding saying  
6 that of the 225 patients. Hold on, I'll read  
7 it for you, I think it's helpful enough.

8 Two hundred twenty five patients  
9 were eliminated because of insufficient data  
10 or unevaluable ECG. And in the remaining  
11 1,500 patients, the available outcome data on  
12 80 lead reading of ST elevation, was  
13 associated with a statistically higher rate of  
14 death, with a high odds ratio of 11 range  
15 compensatable from 1.8 to 67. And a strong  
16 trend toward a higher rate of death and  
17 recurrent MI odds ratio, 3.4, than those of  
18 patients without a reading of ST elevation in  
19 the 80 lead. It's complicated, but I'll  
20 paraphrase it.

21 That they found that of the  
22 patients who -- I'm going to try to make this

1 clear, because it actually is complicated.

2 The patients who were identified  
3 with ST elevations by a prime ECG, had a  
4 higher rate of mortality compared to patients  
5 who didn't have that ST elevation. That was  
6 not found on the comparator of the standard  
7 EKG.

8 DR. GOODMAN: Okay, thank you.  
9 But tell me why -- maybe I'm missing the  
10 point. Tell me why that is causal as opposed  
11 to prognostic? It sounds prognostic as  
12 opposed to causal, correct?

13 DR. COEYTAUX: It isn't causal,  
14 first there's no, we cannot make a causal  
15 inference. And it may be that this data  
16 should not be discussed here. I really don't  
17 know.

18 The reason that we had brought it  
19 up was because one possible explanation is  
20 that there could be a causal connection in  
21 that. It's possible, we don't know.

22 It's possible that the results of

1 the prime ECG resulted in actions taken by the  
2 health care team that lead to changes in  
3 ultimate outcomes. That's possible but we  
4 don't know that.

5 DR. GOODMAN: Or could simply be  
6 that people who had certain test result using  
7 particular technology that you're more or less  
8 likely to die ultimately. Which may have had  
9 nothing to do with how you were treated.

10 DR. COEYTAUX: And that's  
11 absolutely true. And since we don't know  
12 this, I don't want to do the irresponsible  
13 thing by trying to create a causal  
14 relationship when there may not be there.

15 I'm reporting it because I at  
16 least look at that and said, "Hmm, that's an  
17 interesting finding, what could it mean?" It  
18 could mean just straight forward prognostic.  
19 Very high likelihood that it is.

20 But it could also be because of an  
21 actual impact on health outcomes. And we  
22 don't know.

1 DR. GOODMAN: Okay, I appreciate  
2 it. If anybody's got a shred of evidence or  
3 insight that says why that might be causal as  
4 opposed to prognostic I'd be really interested  
5 in hearing it. At least based on what I  
6 heard.

7 Comments from any of our panelists  
8 on this issue, patient outcomes, adequacy of  
9 evidence. Any of our speakers on this issue.  
10 Thank you, let's proceed to vote then.

11 This is Question 7, adequacy of  
12 evidence, how confident are you that there's  
13 adequate evidence to determine whether or not  
14 the use of SAECG technologies, any of them,  
15 significantly improves patient health  
16 outcomes.

17 And I'll remind you that patient  
18 health outcomes were defined in the preamble.  
19 One is low confidence, three is intermediate,  
20 five is high confidence.

21 Thank you. All votes are in the  
22 mean score is 1.125. Dr. Phurrough?

1 DR. PHURROUGH: Steve  
2 Phurrough, one.

3 MS. CABRAL-DANIELS: Rene  
4 Cabral-Daniels, one.

5 DR. HESELTINE: Peter Heseltine,  
6 two.

7 DR. JANOWITZ: Warren Janowitz,  
8 one.

9 DR. MCDONOUGH: Bob McDonough,  
10 one.

11 DR. SAADI: Ryan Saadi, one.

12 MR. SAMSON: David Samson, one.

13 DR. STEINBROOK: Robert  
14 Steinbrook, one.

15 DR. SEAL: Brian Seal, two.

16 MS. ELLIS: Dr. Rudy, two.

17 DR. GOODMAN: Thank you very much.

18 Any comments on this one before we proceed?

19 Because the mean score falls below the  
20 threshold we would not address Question 8.

21 But I don't want to leave this  
22 matter of patient outcomes unless, until

1       you've decided you've got nothing else to say  
2       about it. At this point, why you voted or  
3       anything like that. It seemed like a pretty  
4       uniform vote down the line. Dr. Rollins?

5               DR. ROLLINS: Does adding the  
6       words "lead to" make a difference in terms of  
7       trying to explain the causal relationship as  
8       opposed to the way it sort of seems.

9               Because somebody might say a  
10       diagnostic test in itself is not going to  
11       alter outcomes unless somebody uses the  
12       results of that to change management.

13              DR. HESELTINE: Clearly the  
14       diagnostic tests influence decision making but  
15       obviously don't have direct impact. So  
16       unfortunately when you say improves here, it  
17       would probably better to word that somewhat  
18       differently to imply the indirect benefit.

19              DR. GOODMAN: Let me just submit  
20       that various designs of studies, various well-  
21       designed studies, and not just in RCT can  
22       provide acceptably rigorous evidence, that

1       there's a causal effect. A causal impact of  
2       a diagnostic on a decision and sometimes even  
3       a patient health outcome.

4               So I think improves is certainly  
5       acceptable and feasible here, I think we all  
6       recognize that the improvement is not  
7       necessarily direct. But that doesn't mean it  
8       is not causal. So your point is well taken,  
9       Dr. Heseltine.

10              And Dr. Rollins, thank you very  
11       much, it's possible that it could have a cause  
12       indirectly. But we'd be glad to entertain any  
13       study that's designed to figure that out. Now  
14       that we saw that today. Dr. Steinbrook?

15              DR. STEINBROOK: In terms of the  
16       general subject area, you know, forgetting  
17       about the wording. But you would really want  
18       for adequate evidence a body of studies that  
19       were looking at health outcomes and collecting  
20       in these four different domains that you  
21       mentioned.

22              Whether they're perspective or

1 cohort, or what have you, in terms of study  
2 design. And that's, I think, what we would be  
3 looking for. It didn't seem at least in this  
4 instance that we just had a lot of information  
5 about how health outcomes related to this  
6 technology.

7 DR. GOODMAN: Right, thank you for  
8 your point. Well stated, Dr. Steinbrook.  
9 Yes, Dr. Cabal-Daniels.

10 MS. CABRAL-DANIELS: I'd like also  
11 to point out that when we talk about patient  
12 health outcomes here, I'm assuming the outcome  
13 as defined by the provider. And that we  
14 should also always bear in mind that a patient  
15 health outcome may be defined differently by  
16 the patient, him or herself.

17 DR. GOODMAN: Point well made Ms.  
18 Cabal-Daniels. And I would say that one of  
19 the aspects that we hope is useful about  
20 MEDCAC meetings such as this is to share. Not  
21 just among MEDCAC members and CMS staff but  
22 other stakeholders that.

1           The environment of expectations  
2       for evidence is changing. In general the bar  
3       is kind of rising but it's not just a slightly  
4       rising bar in some cases it's the nature of  
5       the evidence that's changing and patient  
6       reported outcomes.

7           Patient centered outcomes, are of  
8       increasing importance with regard to the  
9       evidence environment. So your point is very  
10      well taken and I would say that's a useful  
11      signal for those who have the job of  
12      validating innovations and other  
13      interventions. Thank you. Dr. Heseltine?

14           DR. HESELTINE: So to that point,  
15      follow on with it. One of the things which is  
16      as physicians we tend to look for a disease.  
17      Patients obviously want to be told they don't  
18      have disease.

19           So studies that are designed to  
20      actually show that the person doesn't have the  
21      disease, which is what patients want. These  
22      are extraordinarily valuable studies.

1                   So some of these technologies  
2                   studies might actually demonstrate that you  
3                   don't have cardiovascular disease or you don't  
4                   have coronary artery disease and that would be  
5                   very, very helpful.

6                   DR. GOODMAN: Rule outs are great,  
7                   yes, Dr. Heseltine. Dr. Janowitz.

8                   DR. JANOWITZ: On that same point,  
9                   I think the point raised earlier that  
10                  avoidance of more invasive studies is also a  
11                  positive outcome that should be investigated.  
12                  Or touted as almost as well as the avoidance  
13                  of mortality.

14                  DR. GOODMAN: Thank you very much.  
15                  And when you kind of look at how you might  
16                  detail patient orientated outcomes avoidance  
17                  of invasive procedure may very well be highly  
18                  preferred by patients. So point well made.

19                  We've already obviously ventured  
20                  into Question 9 without my having had to  
21                  declare it. We've been listening to evidence  
22                  since about 8:00 a.m. this morning.

1                   And having gone through our voting  
2                   questions, we'd very much appreciate if our  
3                   panelists, and I hope something -- at least  
4                   one thing from each panelists regarding gaps  
5                   in evidence.

6                   And the formal question is stated  
7                   as, what evidence gaps exist in the field of  
8                   signal analysis ECG devices?

9                   The reason we're doing this is  
10                  that, keep in mind that there's not a national  
11                  coverage determination on the table. The  
12                  agency is going to be looking at this  
13                  obviously.

14                  Otherwise there would not have  
15                  been this MEDCAC meeting. It's very helpful  
16                  to the agency as well as innovators and other  
17                  stakeholders to understand whether there are  
18                  evidence gaps that could be filled. That  
19                  might provide greater guidance to the medicare  
20                  program as well as to clinicians, patients,  
21                  caregivers and family members.

22                  So panel, what's missing here

1       that's a high priority for being filled with  
2       regard to evidence. Do I have a first taker?  
3       Dr. Seal.

4               DR. SEAL: Coming from a health  
5       outcomes background. The patient reported  
6       outcomes of symptoms and quality of life are  
7       really important in this patient population.  
8       It's one where there's a significant morbidity  
9       and mortality. So that becomes a high piece.

10              So to put some of those  
11       instruments into the trials would be helpful  
12       both to the physician and the patient when  
13       decision making around what the next test is.

14              DR. GOODMAN: Thank you, Dr. Seal,  
15       very helpful. Dr. McDonough is next.

16              DR. MCDONOUGH: Just the point  
17       that's made a lot of times today, how we were  
18       struck that a lot of these studies didn't have  
19       an appropriate reference standard. And that's  
20       something that we need in the future.

21              DR. GOODMAN: Thank you, reference  
22       standard, excellent point. Further points?

1 Mr. Samson?

2 MR. SAMSON: I think it's really  
3 important to figure out what the comparison  
4 ought to be. Is it some series of test and  
5 treat strategy, one of which includes signal  
6 average ECG and another that doesn't? Should  
7 it be head to head comparisons of diagnostic  
8 accuracy on things like SAECG and perfusion  
9 imaging. These things really need to be  
10 addressed.

11 DR. GOODMAN: Thank you, Mr.  
12 Samson. Next point, Dr. Heseltine.

13 DR. HESELTINE: The piece that I  
14 think is missing, that is relevant to all  
15 sorts of studies that we do in diagnostics, is  
16 to actually determine precisely what is the  
17 altered case management that will be done for  
18 this particular patient?

19 Even if it is subpopulation of  
20 patients. Because without that, all you have  
21 is, well I have interesting additional  
22 knowledge, or interesting additional academic

1 knowledge. Or maybe physiologic knowledge.

2 But really it's about altering the  
3 clinicians management of the patient. That's  
4 got to be end point for these studies.

5 DR. GOODMAN: Thank you, Dr.  
6 Heseltine. Ms. Cabral-Daniels.

7 MS. CABRAL-DANIELS: It's like to  
8 build on a number of points made. I hope  
9 that will be approached patients we don't look  
10 at them monolithically. But that we look at  
11 them with the level of sensitivity, that we  
12 have, in other areas.

13 DR. GOODMAN: Thank you. Dr.  
14 Steinbrook.

15 DR. STEINBROOK: I want to make a  
16 slightly different point. This follows up  
17 after a question I ask earlier about the FDA  
18 clearance of the devices which should be FDA  
19 cleared. And what information could be  
20 learned at that time.

21 There's a big debate in this  
22 country right now about the process for

1 getting medical devices on the market.

2 There's been the ILM Report. And a lot of  
3 discussion.

4 But I would just submit for a  
5 group such as this and for Medicare, to the  
6 extent that there is clinically relevant data,  
7 which is generated as part of the process of  
8 getting devices on the market. And cleared by  
9 the FDA, it would really help in terms of  
10 figuring out how to use them.

11 DR. GOODMAN: That is a good  
12 point. Thank you, Dr. Steinbrook, very good.  
13 I believe Dr. Phurrough was next.

14 DR. PHURROUGH: Two or three  
15 things. First of all we had, in the TA  
16 identified, 11 technologies and we found  
17 studies on three. One on one study, three or  
18 four on MCG, and ten of various quality. Only  
19 one really decent one on the prime.

20 So the big evidence gap is,  
21 there's none, for most of these technologies.  
22 That's a gap that goes along with this FDA

1 clearance process, which says, you got to  
2 demonstrate that you can do something similar  
3 to something else, that had no evidence of it  
4 having any benefit. Not that I'm biased  
5 against that particular process.

6 Two, any evidence would be better  
7 than what we have in preventive devices.

8 Secondly, to go on with and expand  
9 on some of the other comments. Too much  
10 clinical study today focuses -- doesn't focus  
11 enough on the needs of some of the end users,  
12 like patients.

13 What do patients really want to  
14 know. What do peers really want to know?  
15 What does Medicare need know to make a  
16 decision? What does United need to know to  
17 make a decision? Focus is many times on what  
18 I need to know to get to the market? Which is  
19 a vastly different question.

20 So there's gaps in the kinds of  
21 information that patients and clinicians and  
22 payers need to know to answer those particular

1 questions.

2           There's an assumption commonly  
3 with many technologies that I need to meet the  
4 standard of the current standard of care. And  
5 that's a false assumption in today's climate.

6           Just because you have as much as  
7 or more evidence than the current standard of  
8 care, doesn't mean it's any good. And so,  
9 yes, new technology has a higher bar. Live  
10 with it. That's the way it is.

11           And then finally it's just the,  
12 you know, issue of diagnostics, it's just got  
13 to move beyond. You know the sensitivity,  
14 specificity, characteristics, those are just  
15 not adequate. Regardless of whether they  
16 exceed statistically or in other manner.  
17 Those of current technologies, you've got to  
18 demonstrate that your technology changes  
19 things.

20           Preferably changes patients  
21 outcomes. That is difficult and in some cases  
22 there are other studies that clearly

1 demonstrate that a particular intermediate  
2 outcome will in fact change the end outcomes  
3 that we're interested in.

4 But that's got to be a pretty  
5 clear process that's already developed. Any  
6 thinking that says I need to get my  
7 sensitivities specificity data and my  
8 characteristics, diagnostic characteristics  
9 data out there. And that's enough. That  
10 really is just insufficient in today's market.

11 DR. GOODMAN: Thank you, Dr.  
12 Phurrough. Dr. Saadi.

13 DR. SAADI: I was actually going  
14 to repeat, not as well as you actually you  
15 did, Dr Phurrough. That's actually our  
16 precise challenge here. That this an  
17 observation I would like to make this comment,  
18 for the record, this comment that the industry  
19 folks, and I'm part of it, as you know. That  
20 we actually have a different expectations from  
21 the FDA.

22 And it actually comes to CMS. Or

1 any peer globally. It's actually completely  
2 different. So the part actually I think is  
3 missing, that the industry folks, we don't  
4 quite see it. It's a very, we have a very  
5 clear understanding, we have in house experts.  
6 In terms of how to satisfy FDA.

7 And we actually have very limited  
8 understanding. How to satisfy any payer  
9 including the CMS, of course.

10 And now people like me are, and  
11 Dr. Harland, obviously you know that. But  
12 that's not actually enough. So I think that  
13 something in there, I think should be  
14 discussed here or at least addressed. Or CMS,  
15 you actually need to send the signal out, hey  
16 guys, listen, this is actually the new  
17 reality.

18 DR. GOODMAN: Thank you, Dr.  
19 Saadi. As I think I suggested earlier, I  
20 think that you're highlighting. Meetings like  
21 this help with that changing environment, make  
22 that changing environment explicit to the

1 innovators as well as others.

2 I would add that on occasion  
3 innovators can come to CMS for early meetings  
4 to discuss mutual evidence expectations. And  
5 those are often very helpful meetings.

6 Further points on evidence gaps,  
7 Dr. Phurrough.

8 DR. PHURROUGH: We've been sort of  
9 talking the researches and I'll turn around  
10 and talk to CMS a bit. Something that covers  
11 doesn't have an option really but because I've  
12 worked here long enough I can say what I  
13 think.

14 The real gap that researchers have  
15 is knowing what the bar is. You know, FDA  
16 fairly good at telling you what the bar is.  
17 CMS says we'll let you know what the bar is  
18 after we make out decision.

19 Which is pretty tough. We says we  
20 want adequate evidence, well what's adequate?  
21 I've lived with that, I recognize that there's  
22 challenges in doing that.

1 But they need to grow up. It's  
2 not a coverage issue, it's a CMS issue.  
3 Actually a department issue, of deciding that  
4 there needs to be some clearer guidance that  
5 says, here's what we expect for us, for you to  
6 bring to us, so that we can make a reasonable  
7 decision based upon that.

8 DR. GOODMAN: Thank you, Dr.  
9 Phurrough, with your view from the inside as  
10 well as the outside. Ms. Cabral-Daniels.

11 MS. CABRAL-DANIELS: I would like  
12 to piggy back on that with regard to enhanced  
13 transparency of the agency, not only benefits  
14 researchers, but I think it would help the  
15 patient population also.

16 DR. GOODMAN: Transparency. Thank  
17 you. Further comments on -- yes, Dr. Janowitz  
18 on evidence gaps.

19 DR. JANOWITZ: Yes. I think what  
20 has to be done in my view, is really focus on  
21 what this technology is potentially used for.  
22 I don't think it's ever going to replace

1       biomarkers. I don't think it's ever going to  
2       replace angiography.

3               But where it has a potential role  
4       is in this whole bunch of intermediate tests,  
5       which currently exist to determine which  
6       patients get referred on for further testing.

7               Any time you have four or five  
8       different competing modalities to determine,  
9       you know, the patient's next step. I think  
10      there's room for potentially developing a  
11      better test.

12              So if this technology could be  
13      better at determining who has to go on for  
14      more invasive procedures. I think that is a  
15      good niche for it. To try and make it do  
16      everything, it's just not going to happen.

17              DR. GOODMAN: Thank you, Dr.  
18      Janowitz. Further points on evidence gaps.  
19      Are there any of our speakers today who in a  
20      concise way would want to indicate or point to  
21      an evidence gap or comment regarding an  
22      evidence gap?

1                   Just to capture your insights for  
2                   the agency and others. Yes, Dr. Strobeck.  
3                   Welcome back to the microphone.

4                   DR. STROBECK: Thank you very  
5                   much. No, I just really would like to echo  
6                   the comments of Dr. Janowitz. I mean we need  
7                   to focus on specific areas. And I think the  
8                   area of highest importance, at least from my  
9                   point of view as a practicing cardiologist, is  
10                  really making evidentiary based decision on  
11                  which diagnostic test to do.

12                  Many patients are getting two or  
13                  three diagnostic tests, because of the  
14                  inaccuracy are being, essentially loaded with  
15                  testing prior to the gold standard test, which  
16                  they ultimately get anyway. And if we can  
17                  have an accurate way of determining who needs  
18                  that invasive strategy. I think that makes a  
19                  big difference. That's what we're going to  
20                  try to do. Bring back that kind of evidence  
21                  base.

22                  DR. GOODMAN: That's great. Thank

1       you very much, Dr. Strobeck. Yes, Dr. Imhoff.

2               DR. IMHOFF: Well it was mentioned  
3       somewhat before, but I would like to express  
4       that it is extremely important when we're  
5       talking about myocardial ischemia. We need to  
6       have an accepted gold standard for myocardial  
7       ischemia and not only for the morphological  
8       change and the morphological CADDIC's.

9               And that is something where the  
10       panel or CMS or other agencies may make a  
11       strong recommendation what is considered a  
12       gold standard test for myocardial ischemia.

13              Because in the literature we also  
14       have the problem that it is very difficult to  
15       agree on that. Also for instance with the  
16       FDA, I had discussion recently.

17              DR. GOODMAN: Good, thank you for  
18       your comment Dr. Imhoff. Yes, gold standard  
19       for myocardial ischemia. Greater  
20       clarification. Yes, Mr. Leisy.

21              MR. LEISY: If I could just speak  
22       on behalf of one of our team members, Dr.

1 Galen Wagner, who's a specialist in  
2 electrocardiography and journal and editor for  
3 the journal for the electrocardiography,  
4 directed a lot of our discussion on the  
5 certain technologies and devices in there  
6 applicability today.

7 He spoke specifically about the  
8 body surface mapping device, which began  
9 development about ten or 15 years ago. Prior  
10 to this thought of spending the equivalent,  
11 which is only a very recent idea.

12 And he said his argument was that  
13 back when it was first designed a lot of the  
14 STEMI's, the ST elevation that they found were  
15 on the posterior leads. Which now the AHA has  
16 realized that ST depression on the anterior  
17 leads V1 through V4 would show ST elevation a  
18 posterior side.

19 And so he says that, perhaps some  
20 of the data could be skewed because they would  
21 accept. Because the body service mapping  
22 would increase ST elevation, based on the

1       STEMI equivalent criteria.

2                   And I think the gap is that, is  
3       there another application for today's  
4       technology where you can use that information  
5       without developing any new devices.

6                   DR. GOODMAN:   Good.   Thank, you.

7                   MR. LEISY:    You're welcome.

8                   DR. GOODMAN:   Sometimes you  
9       develop a device for purpose A and purpose B  
10      emerges.   Thanks.   Yes, Dr. Janowitz.

11                  DR. JANOWITZ:   Yes, I'd just like  
12      to make a couple of comments about the gold  
13      standard for perfusion.   This is what I do  
14      everyday.   If I had to say right now with the  
15      gold standard that we have available  
16      non-invasively would be cardiac PET.   Next  
17      would be cardiac SPECT with attenuation  
18      correction.

19                  And potentially in the future  
20      coronary CTA with non-invasive detection of  
21      fractional flow reserve, which is a study  
22      that's currently going on.   So, you know, if

1 anyone else has any better ideas, I think that  
2 is where we are right now.

3 DR. GOODMAN: Great. Thank you.  
4 Okay. I think that's it for evidence gaps.  
5 We're not done actually. I'll try to simplify  
6 this. We have a final question that has to do  
7 with generalizable or external validity. I'll  
8 just ask you to kind of integrate under the  
9 curve here. We don't have to get granular  
10 about this.

11 But we've talked about a set of  
12 evidence questions that we've graded on a  
13 Likert scale. We talked about evidence gaps.  
14 It's important for the Medicare program to  
15 understand whether or not there is any  
16 differentiation between what you saw in the  
17 evidence and what might be applicable first to  
18 the Medicare population.

19 So did you see or hear anything  
20 today that raises a flag, or is a special  
21 consideration regarding how useful the  
22 evidence that is available is applicable in

1 particular to Medicare beneficiaries. That is  
2 the disabled and those, typically those  
3 disabled or greater than age 65.

4 Any points to be made about any  
5 differentiation there? Age, group, or  
6 disability? Dr. Phurrough.

7 DR. PHURROUGH: So if we say  
8 there's not adequate evidence to draw  
9 conclusions on most of these questions, can we  
10 even answer this question?

11 DR. GOODMAN: Well, thank you for  
12 posing that. It's possible that while the  
13 evidence overall was not adequate. It's  
14 possible that there might have been a bit of  
15 it that was directly relevant to Medicare  
16 population.

17 Or in the limited cases where we  
18 found adequate evidence, it was -- I think  
19 only one, that might have been more or less  
20 relevant to a Medicare patient.

21 The tone of your question, I agree  
22 with this. Not allowed it to go on in the

1 first place. So how can we conclude  
2 otherwise. But just wanted to provide the  
3 opportunity. So any additional bit on that,  
4 Dr. Phurrough?

5 DR. PHURROUGH: No.

6 DR. GOODMAN: Point well taken.  
7 Dr. McDonough.

8 DR. MCDONOUGH: I interpreted that  
9 question a little bit differently, I mean, in  
10 many cases you're concluding that you're  
11 uncertain and I just assume, and maybe I'm  
12 wrong, that to the extent that these studies  
13 might involve patients in the Medicare  
14 population. Your uncertainty would extend to  
15 them.

16 So you're confident or have some  
17 confidence that your conclusions about  
18 uncertainty would apply to the Medicare  
19 population as well.

20 DR. GOODMAN: That's also correct.  
21 And is there anything that you've seen that  
22 would go against that? About uncertainty.

1 We're uncertain about the body of evidence and  
2 therefore you're saying we --

3 DR. PHURROUGH: I don't, I mean a  
4 lot of these studies seem to be, in my  
5 opinion, you know, a lot of them look like in  
6 older populations that would be served by  
7 Medicare.

8 DR. GOODMAN: Yes. Dr. Heseltine,  
9 you've reversed, but go right ahead.

10 DR. HESELTINE: So the way I read  
11 that question is, are you confident that these  
12 conclusions, which are our answers to the  
13 questions. Are applicable or generalizable to  
14 the two populations in question.

15 DR. GOODMAN: Yes.

16 DR. HESELTINE: So the fact that  
17 we found the evidence wasn't enough in many  
18 cases. The question here is, am I confident  
19 that that conclusion, that there wasn't enough  
20 evidence, is applicable. And so I thought  
21 that was to be in the affirmative.

22 DR. GOODMAN: If the findings that

1       you made today, how confident are you that the  
2       findings were made today, apply to Medicare  
3       population? And if it's affirmative, that  
4       means that, yes, what we said in general  
5       applies to Medicare people.

6               DR. HESELTINE: Right. Because  
7       you could answer their question the other way  
8       and say, that negative we had insufficient  
9       result, therefore we have insufficient  
10      evidence for that population. So I just  
11      wanted to make sure.

12             DR. GOODMAN: No. Thank you for  
13      your interpretation. Let me ask for a  
14      clarification. I don't see a Likert scale on  
15      my scoring sheet for questions. And I thought  
16      it was a discussion question, and not a  
17      grading question. And typically in the past -  
18      -

19             (Off microphone discussion)

20             DR. GOODMAN: One of the scoring  
21      sheets has it, one doesn't?

22             MS. ELLIS: Right. Well, the one

1       that you have is just the regular voting  
2       questions. But the one that the panel members  
3       have is the actual score sheet, because they  
4       actually vote.

5                 DR. GOODMAN: Okay. So you would  
6       like a vote on this.

7                 MS. ELLIS: Yes, we need to vote.

8                 DR. GOODMAN: Okay. I apologize  
9       then. The ones I was looking at had scoring  
10      for everyone, but not this one. Okay. Panel,  
11      I apologize then. We do need to vote on this  
12      one.

13                MS. ELLIS: Yes.

14                DR. GOODMAN: Oh, my apologizes,  
15      it was not in front of me. Dr. Seal.

16                DR. SEAL: I'm hearing both ways.  
17      So one is saying that we're applying the  
18      evidence to this population. Most of the  
19      trials that I saw had 50 percent of the  
20      population was a Medicare population. Which  
21      is higher than a lot of the other trials in  
22      drug trials. Then most of the trials that I

1 saw that they had presented came from  
2 community centers.

3 So just the fact that they have  
4 the evidence, or at least it's not powered for  
5 that. But enough to show that this is where  
6 the patients came from, is important.

7 But I'm trying to decide how  
8 confident are you that these conclusions are  
9 generalizable too. How are we interpreting  
10 the question?

11 DR. GOODMAN: You've drawn some  
12 findings today or some conclusions today about  
13 adequacy of evidence, what the evidence says.  
14 Whether it was strong evidence or weak  
15 evidence, or if the evidence showed something  
16 or it didn't. How confident are you that,  
17 that set of findings applies in particular to  
18 the Medicare patient population?

19 And as you just pointed out, a lot  
20 of these studies probably did include Medicare  
21 eligible patients. So if you're highly  
22 confident that our findings today applied to

1       them, you'd say something like a four or five.  
 2       If you weren't confident, if there was a big  
 3       gap between the available evidence and what  
 4       needs to be known about Medicare population,  
 5       you'd probably score at the bottom of the  
 6       scale.

7                   DR. SEAL: Yes, my thought is that  
 8       even if we scored say a lower number on one of  
 9       the earlier questions, it still applies to  
 10      this population.

11                  DR. GOODMAN: Yes. Which means  
 12      you'd be highly confident that perhaps  
 13      inadequate evidence still applied here. That  
 14      would push you to the top and the other  
 15      instance it would push you toward the bottom.

16                  Thank you. Dr. Phurrough.

17                  DR. PHURROUGH: So the conclusions  
 18      are the panels conclusions. Not the  
 19      conclusions of the research that we have  
 20      reviewed? It's the evidence that we've  
 21      reviewed.

22                  DR. GOODMAN: Correct. How

1       confident are you? Correct. All right, so  
2       once again, I apologize for not having a score  
3       sheet in front of me for this question.

4               Let's take Question 10A. How  
5       confident are you that these conclusions are  
6       generalizable? No matter what your findings  
7       were, no matter what your conclusions were.  
8       How confident are you that those conclusions  
9       are generalizable to the Medicare patient  
10      population?

11             If you're not confident about the  
12      generalizability, that's closer to the bottom  
13      of the scales. If you are confident, closer  
14      to the top of the scale.

15             And I see a 3.875. Thank you very  
16      much. Dr. Phurrough.

17             DR. PHURROUGH: Steve Phurrough,  
18      five.

19             MS. CABRAL-DANIELS: Rene  
20      Cabral-Daniels, four.

21             MS. ELLIS: Peter Heseltine, four.

22             DR. JANOWITZ: Warren Janowitz,

1 four.

2 DR. MCDONOUGH: Rob McDonough,

3 four.

4 DR. SAADI: Ryan Saadi, four.

5 MR. SAMSON: David Samson, three.

6 DR. STEINBROOK: Robert

7 Steinbrook, three.

8 DR. SEAL: Brian Seal, four.

9 MS. ELLIS: Dr. Rudy, three.

10 DR. GOODMAN: Okay. Thank you all

11 very much. Excellent.

12 Now let's ask the same question,

13 10B, for community-based settings. The

14 rational behind this is that sometimes

15 evidence is generated in settings that are

16 ideal, or highly protocolized, or

17 well-controlled, or well-managed, unusual and

18 so forth.

19 And we care about how things,

20 Medicare programs cares about how well things

21 work in the real world. i.e., community-based

22 settings or real world settings. Dr.

1 McDonough, question.

2 DR. MCDONOUGH: Maybe an obvious  
3 one, community settings in the United States?

4 DR. GOODMAN: Yes, sir. One well  
5 made. Okay, let's vote on that. Highly  
6 confident, five. Not confident at all, one.  
7 Intermediate confidence would be a three. I  
8 see a 3.625. Dr. Phurrough, your vote.

9 DR. PHURROUGH: Five.

10 MS. CABRAL-DANIELS: Rene  
11 Cabral-Daniels, four.

12 MS. ELLIS: Peter Heseltine, four.

13 DR. JANOWITZ: Warren Janowitz,  
14 four.

15 DR. MCDONOUGH: Bob McDonough,  
16 three.

17 DR. SAADI: Ryan Saadi, three.

18 MR. SAMSON: David Samson, three.

19 DR. STEINBROOK: Robert  
20 Steinbrook, three.

21 DR. SEAL: Brain Seal, four.

22 MS. ELLIS: Dr. Rudy, three.

1 DR. GOODMAN: Great. Thank you  
2 very much. Okay. We're going to have a few  
3 closing comments, but, Ms. Ellis, if I'm not  
4 mistaken, we've covered all of our questions.

5 MS. ELLIS: That's correct.

6 DR. GOODMAN: Voting and non  
7 voting. All right then.

8 Does anyone who was a speaker  
9 today, before we go to panel, does any speaker  
10 have a final, well-phrased, concise comment,  
11 that they want to make before we adjourn for  
12 the day. Actually go back to our panel for  
13 final comments.

14 Anything that should be on the  
15 table, that's not. Any major important thing  
16 that we missed, that you haven't all ready  
17 cited? Okay. Seeing none.

18 Final comments and, I'll -- we'll  
19 do a forcing function here. Dr. Seal, we're  
20 going to start with you and just go right down  
21 the row here. If you've already said  
22 something that you want to lay with us, don't

1       need to repeat it, that's fine. But any final  
2       closing comments. What's your last word, Dr.  
3       Seal?

4                 DR. SEAL: The technology seems  
5       like it is very useful. In my opinion some  
6       additional studies are required to see where  
7       we could fit it into sighting and into the use  
8       with the medical practice.

9                 DR. GOODMAN: Thank you. Dr.  
10       Steinbrook.

11                DR. STEINBROOK: Well, just talk  
12       about it, the improvements on the standard  
13       12-lead EKG would be welcome. And I think  
14       despite some of the overall conclusions here  
15       today, in terms of where the evidence is now,  
16       that there are ample opportunities and I  
17       encourage people are working on this to keep  
18       going.

19                DR. GOODMAN: Yes. Thank you, Dr.  
20       Steinbrook. Next will be Mr. Samson. Mr.  
21       Samson.

22                MR. SAMSON: Nothing to add.

1 DR. GOODMAN: Thank you. Dr.  
2 Saadi.

3 DR. SAADI: Just one quick thing  
4 is that for industry this is important to  
5 recognize one priority. That the evidence,  
6 the definition of evidence they could be  
7 different. Between CMS and FDA.

8 DR. GOODMAN: Thank you. Dr.  
9 Saadi, Dr. McDonough.

10 DR. MCDONOUGH: I guess on that  
11 point, I mean the evidence standards might be  
12 a little bit different with private peers and  
13 CMS, I mean, obviously we're dealing with a  
14 somewhat different population.

15 DR. GOODMAN: Thank you, Dr.  
16 McDonough. Dr. Janowitz. Any final comments,  
17 sir.

18 DR. JANOWITZ: No.

19 DR. GOODMAN: None by Dr.  
20 Janowitz. Ms. Cabral-Daniels.

21 MS. CABRAL-DANIELS: I would like  
22 to direct my final comments to the Agency, and

1       that would be to encourage the paradigm shift  
2       in terms of looking at different stake  
3       holders, and when looking at the questions.

4               DR. GOODMAN:   Great.   Thank you.  
5       Dr. Phurrough.

6               DR. PHURROUGH:   I think there are  
7       some significant potentials here in this  
8       technology.   I think MCG appears to be moving  
9       in a positive direction for data collection.  
10       Unfortunately we didn't have a lot of that  
11       data to review, since one of the main ones is  
12       a recent study.

13               I think that's encouraging, and  
14       hopefully as these other technologies.  
15       Hopefully these other technologies will also  
16       take the time to develop the evidence base  
17       that makes patients and payers and clinicians  
18       more comfortable with the technology.

19               DR. GOODMAN:   Great.   Thanks Dr.  
20       Phurrough.   Before I turn it back over to Dr.  
21       Rollins.   A few other closing comments.

22               First, today we saw, we've seen

1 available evidence, as best we could. In this  
2 instance there were few studies. Most of them  
3 were not very strong. Or I should say in  
4 general, the body of evidence was not very  
5 strong.

6 We did look for the best evidence,  
7 and that is an important phrase, best evidence  
8 where we could find it. It wasn't the best of  
9 evidence. But we did make some specific  
10 findings. I would reiterate that MEDCAC can  
11 only appraise the evidence that's brought to  
12 it.

13 And whether that's a matter of  
14 timing. That's one issue, whether it's a  
15 matter of not being in the peer reviewed  
16 literature. Whether it's a matter of being,  
17 not being in inclusion criteria for a  
18 technology assessment or systematic review.  
19 We can only deal with the evidence brought  
20 before us.

21 And so just a point to be made to  
22 innovators, industry and so forth, is that to

1 the extent you can anticipate the kind of  
2 evidence that policy makers may need. Or  
3 other decision makers may need. Or evidence  
4 appraisers may need. You want to be ahead of  
5 the curve, not behind it. We can only  
6 appraise what's in front of us.

7 Next, there is a difference.  
8 There are many differences between FDA  
9 expectations, or any regulatory agencies  
10 expectations. And the needs of coverage  
11 decision makers. And as Dr. McDonough pointed  
12 out, there are different needs among Medicare,  
13 state Medicaid, commercial insurers, and so  
14 forth.

15 And honestly from the stand point  
16 of innovators, they've got to deal with  
17 multiple regulators around the world, and  
18 multiple payers. So it's not an easy road to  
19 hoe there. But there are distinct  
20 differences.

21 Next, when you deal with screening  
22 tests, diagnostic tests, it's just not enough

1 anymore to show that you've got a sense of  
2 this specific test performance.

3 Characteristics are necessary. But they are  
4 no longer sufficient.

5 While it is sometimes difficult,  
6 but not always, to draw lines from a test to  
7 a finding that's reliable. A finding to a  
8 decision, and a decision to help outcome.  
9 That's what we're seeking more and more.

10 It's not just the Medicare  
11 program, I can assure you. It's health  
12 authorities around the world, in the public  
13 and the private sector. This is not just  
14 something that Medicare does. In fact in some  
15 ways Medicare's trailing a little bit on the  
16 insistence for that kind of, for that kind of  
17 evidence.

18 And by the way, the more you come  
19 to meetings like this or watch their results,  
20 or similar kinds of meetings that appraise  
21 evidence. You're going to see the same thing  
22 over and over.

1 More and more, decision makers,  
2 and I don't mean just peers. Patients,  
3 clinicians, and others are saying more and  
4 more, we want, real world evidence. Not just  
5 eye evidence from idealized settings. We want  
6 to have comparators. Real comparators, real  
7 world comparators.

8 And we care about health care  
9 outcomes. And more and more within health  
10 care outcomes, we care about patients centered  
11 or patient oriented outcomes.

12 This is a consistent message  
13 you're going to hear over and over. If you  
14 think you heard it today, I wish it wasn't the  
15 first time you heard it. But I can promise  
16 you also, it won't be the last time you're  
17 going to hear it.

18 So I think this is was a very  
19 helpful day today for our panelist. Thank you  
20 all very, very much for your effort. All the  
21 way up and down the line. Thank you very much  
22 for the attention, the homework you had to do

1 leading up to this. Thank you very much for  
2 our guest speakers, all of you.

3 Especially those of you that  
4 stayed for the entire day. And were most  
5 attentive and were highly, and specifically,  
6 and insightfully responsive, to our quite  
7 diverse questions.

8 I know it takes lot to go through  
9 a day like this. I know your day started very,  
10 very early. We very, very much appreciate on  
11 behalf of MEDCAC and the agency. Your  
12 presence and willingness to take part in this.

13 We are further very much  
14 appreciative of the technology assessment  
15 team, for Evidence Based Practice Center. In  
16 particular Dr. Coeytaux and Mr. Leisy, for  
17 standing and sitting so very frequently and  
18 coming up with these excellent responses.

19 Thank you very much as well to  
20 Lisa Eggleston for her initial presentation  
21 for voting questions and so forth. Thank you,  
22 Dr. Miller, Dr. Rollins, Ms. Ellis, for making

1       sure that everything runs smoothly on time.  
2       People come and go as they need to. With that  
3       I'll turn it over to Dr. Rollins.

4                 DR. ROLLINS: Let me just say that  
5       I would like to echo everything that the panel  
6       members have said. And as I said earlier  
7       today, MEDCACs basically serve a number of  
8       purposes. Number one, we can get information  
9       from experts in the field. And number two, be  
10      able to disseminate this information to the  
11      general public.

12                I'd like to thank the members of  
13      the MEDCAC committee. Especially the  
14      chairperson, the vice-chair person, as well as  
15      the speakers and everybody else in the  
16      audience for participating in this afternoon  
17      and this mornings discussion. Thank you.  
18      Thank you all.

19                DR. GOODMAN: I guess we are  
20      adjourned.

21                (Whereupon, the above-entitled  
22      matter went off the record at 3:10 p.m.)

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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.

  
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Court Reporter

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