

CENTER FOR MIND-BODY MEDICINE
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CONCURRENT: New Research on Mind-Body Interventions

SPEAKERS: ALASTAIR CUNNINGHAM, Ph.D. Ontario Cancer Institute; PAMELA GOODWIN, M.D. Marvelle Koffler Breast Center

COMMENTATOR: JULIA ROWLAND, Ph.D. National Cancer Institute

MODERATOR: Stephen Sagar, MD Hamilton Regional Cancer Centre

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PROCEEDINGS

DR. SAGAR: We'll introduce the following speakers: Alastair Cunningham is a psychologist and senior scientist at the Ontario Cancer Institute in Toronto and Professor of Medical Biophysics and Psychiatry at the University of Toronto. Over the last 20 years, he's developed and researched a multi-stage program of group psychological therapy for cancer patients and their family members. He's published numerous papers on Mind-Body Medicine and the clinical outcomes of his program, and he's a regular contributor to the wonderful journal, *Advances, The Journal of Mind-Body Medicine*. The second speaker will be Pamela Goodwin. Dr. Goodwin is an Associate Professor of Medicine at the University of Toronto. She's a senior scientist in the Samuel Lunenfeld Research Institute at Mount Hospital and holder of the Marvelle Koffler Chair in Breast Research. Dr. Goodwin's research activities focus on the investigation of lifestyle factors in breast cancer, and she is the principal investigator of studies and investigate the interaction between nutrition, body size, exercise, and various physiological mediators such as insulin in breast cancer. But her main focus today is on the innovative best study, which is an expressive support group study which is modeled on David Spielberg's support groups. And this was the first -- the first multi-center randomized trial which investigated the effects of group therapy on survival in metastatic breast cancer. And our honorary Canadian today is Julia Rowland, who is Director of the Office of Cancer Survivorship at the National Cancer Institute. She's been active as a physician, researcher, and teacher in the area of psycho-social aspects of cancer for more than two decades and has worked with Dr. Jimmie Holland in the field of psychooncology, spending 13 years in psychooncology at Memorial Sloan-Kettering, and has the challenging task, once again, of being the commentator for this session and summarizing and questioning some important points that the presenters have made. So without further adieu, I'd like to introduce Dr. Alastair Cunningham.

DR. CUNNINGHAM: Steven, thank you very much. What I'll talk about first is sort of generally about the two main methods, kinds of methods that are being used to study this question. And then I want to -- in the second part I'm going to discuss our results with a new kind of approach, which is a kind of combination of these two methods. The experience I've been drawing on is my original training, which is in cell biology, to some extent, and then later training in clinical psychology, 20 years of conducting a large program at the -- at a cancer hospital in Toronto, and my own cancer 14 years ago, serious cancer in which I took very strong steps to recover from,

with the help of medicine. So the next -- the first slide. I want you to look at just the basics first of all. This is the pathway. I think we're interested in asking, is there some state or event of the mind that could improve survival duration of people with cancer, it's like a fundamental question. And that appropriately shows that there are pre-existing qualities in the mind and they may change under the impact of the diagnosis, it's important to think that they do. In terms of this black box, regular mechanisms, and still not well understood what regulates cancer, and I was in that kind of research for many years as an immunologist, and I think -- I think people doing it still don't understand exactly what regulates cancer, something certainly does. Cancer itself, if you can see at the back, and then life span, the -- the final outcome, if you'd like, or one of the final outcomes at the bottom of the pathway. Now, there's some point -- one particular point to keep in mind as we think about this question, about the basics of biology of cancer, when it's detected, it's not like the flu, it's been there for months, perhaps years. It's been a process of Darwinian selection, evolution of selection of new cells in the body. By the time we find it, the cells that are there are quite happy in that person's environment, whatever that might be, otherwise they would have gone. So it follows that if the mind is going to effect to change the rate of growth, there's got to be a change in mental state, sufficiently great to effect -- effect the black box regulators, and so to effect the rate of progression of the disease and -- and ultimate survival. Bear that one in mind and we'll come back to it. Two main strategies are being used to investigate whether the mind can effect cancer progression and survival. The first is intervention trials, not the first historically, it's a more recent approach, but one that might come to your mind first of all, to use an intervention and to go straight from the top of that path right to the bottom. In this, the intervention is typically treated like a drug, it's all that kind of methodology. And you ask whether the application of the therapy can improve survival. The main limitation, as I'll discuss, is little attention is paid in that -- with that design to what's happening with individuals, relatively little. The second approach and the old approach, older approach, correlative studies, sometimes -- sometimes called with derogatory tone, exploratory studies, as in that's only an exploratory study. They relate -- they -- they try to relate what's happening in the mind, the state of the mind, to life span, let's say. Historically, those studies have not incorporated an intervention, so if you bear in mind what is it about the cell biology, you'll see why it's not surprisingly having come up with a consensus about what states promotes ----- . You need an intervention, because whatever the person's state of mind is at the time of diagnosis, unless it changes, the rate of change of growth is not going to be influenced by the mind very much, I don't think. We've got some important points. Julia may disagree, and I hope she'll think about giving her views. So the two main strategies, just to show them on the slide, intervention trials, which is a verification approach, and asks a very specific question, does this intervention, X, effect the life span of this population of patients, Y, under condition, Z, if you like, or Z. And the -- the analysis is a statistical comparison of groups, millions and millions of groups. Correlative studies, more exploratory in nature, you're asking what psychological qualities correlate with, or are associated with living longer. You know, since each individual is characterized and his or her outcome looked at. Both of them have their uses, but they ask very different kinds of question. My main argument today is that we're at a very early stage of understanding healing, and particularly healing from cancer through the mind, and we need to use, I think, correlative observational methods more than we have done in the past. We've used both approaches in our institute. And in my experience, I have not learned very much from the trials approach. I have learned a great deal from the correlative approach. So I want to contrast the -- now the two sets of results that we've obtained from the two approaches in our experience. Next one, please. We

did a study ...Dave likes to say it was too small, but in fact, there were a few more patients than he had by the time you count the drop-outs. And we got -- we got -- we got no difference in survival. These are women with metastatic breast cancer receiving a year approximately of group therapy, and that's the survival curve, Kaplan Meier curve, and with no significant difference between the blue intervention group and the red control groups. The actual cure mapped pretty much on the Spiegel intervention curve. It was a very similar intervention to Dr. Spiegel's. We hired a group therapist for this, a conventional group therapist, I wasn't the therapist. It was supportive, expressive in nature, with the addition of some training and coping skills. The next -- things got even worse when we repeated the analysis. They don't get much closer than that. This as we repeated the analysis using time for metastatic diagnosis to death. The curves had no difference we could see. So our conclusion was that -- we were pretty disappointed. Back in the days of the early '90's, we were hopeful that maybe group therapy would -- would be something that would prolong the life of most people with breast cancer, at least. Our conclusion was that there was no effect. This was the first study done and the first randomized trial designed to test the question. And Pam is going to share a much bigger study which comes to something of the same result, I believe. And we concluded that the Spiegel result was a chance effect as Bernie Fox had argued long ago. So we -- we have fortunately now another study from Pam Goodwin and she's going to tell you about it, a big, well conducted study, extremely valuable, and it gives this result also. And I think -- we'll see -- and Pam will say whether she agrees or not. I think you're going to conclude that the main effect of this kind of therapy on women with metastatic breast cancer is small, it cannot be large. That's about the limit of the conclusions you can draw. The next slide. There are 11 such trials now, mostly randomized trials. Five have given positive results, six have given negative results I won't go into them any longer. But we are at a bit of an impasse. I don't think we really know quite what to -- what to think for sure about this. Because of our training, most of us tend to think first of randomized trials. Most of us researchers in this area think first of randomized trials. We might ask now, are there some limits to this approach, because I'm sure there are many of you in the audience who are -- who are therapists and healers and have a sense that people who get very involved with their self-care and so on do much better, as I always had after 20 years of watching people. And so you start to conclude, well, maybe science is not showing what I see, so how can we resolve this conflict? Let's look first at the limits of randomized trials, the next one. Randomized trials were first designed for agricultural plots, and then they're applied to drugs, and they fit quite well in drug testing work. And stage III trials comparing an intervention with a control or another intervention, tend to be done only after a number of preliminary experiments, phase I or phase II, by which time you already know quite a lot about the drug or intervention under test, know how it works, and the aim is to compare it with the previous best therapy. None of that stage, I don't -- I see now, I didn't see this clearly 10 years ago, but I've seen a lot of that stage with healing. We don't really know what therapies can induce what stage in people, at least as researchers we don't, therapists have good ideas. And a major problem with using the RCT in this kind of research is that it -- it ignores the great variability between subjects. Now, anyone who's run a class teaching meditation or something to patients knows that about 10 to 20 percent do it, a few more do a bit, and the rest don't do anything, let me put it brutally. If you lump them all together, the mean doesn't -- the mean doesn't mean very much. The -- the efforts of a few are diluted out by the apathy of the many in many cases. So that -- that's a severe problem, I think, in using the sort of methodology and subjecting psychological and psychotherapy to trials methodology, and that's not just my opinion, that -- that is quite a substantial opinion within the group of people who do

psychotherapy outcome research for many things other than cancer. It can lead to what -- what is called a Type II error, assuming there's not an effect when there may be one. And I think we're going to see that when Pam's study comes out. I think we're going to see critics hopping on that and saying let's put to rest the myth that the mind has got anything to do with cancer. I'm afraid that's going to happen, and I don't think it's justifiable to draw that conclusion, but nevertheless, it probably will be drawn. I doubt if we can settle the issue with more and more randomized trials. I think we need a different approach. Is there another way? We don't have to be sheep. We don't have to allow statisticians to dictate to us how we can do our research, at least not entirely. They're very useful, of course. So let's have a look at the next one. Correlative approach, the big limitation is, it's hard to know if it's causal, and you see an association. Is it really causal? Is the intervention really doing it? And we have to acknowledge that, so severe limitation of that approach. It's also very difficult to characterize subjects adequately, and that's true of any approach. And there have been two -- there have been two kinds of problems with this approach. First of all, historically, no intervention has been used, as I already said, so the cancer is growing happily in an angry person, if they stay angry, it doesn't change. Cancer is growing in a depressed person, if they stay depressed, it doesn't change. So you need an intervention and that's not been done in a lot of the correlative work. The other difficulty is being this one of psychological characterization. And the -- the usual thing has been to use psychometric self report scales just to not get under the defenses of the people. They give you very superficial, very unreliable answers that don't correlate well with one's clinical observations. You can obtain detailed characterizations of people ----- descriptions, but it's laborious, as you'll see when you see how laborious we sit. So I'll summarize this part of my talk by saying I like to divide CAMS into internally assisted and externally assisted methods of healing. They're very different. It's perfectly appropriate to teach -- to -- to research things like antioxidants with -- with trials methodology. It's not so clear that when you want to assess psychotherapy, that people are very variable in their dedication today ----- to use the best approach. You need one maybe at the very end of your series of experiments, but maybe not at the beginning. So I want to show you now the results of a strategy that tries to combine the best features of both approaches, I hope. We decided to follow a small number of patients one by one in a rigorous way related psychological change to -- to survival outcome. So it's basically correlated. We incorporated an intervention, however, to make change more likely. Now, this approach is not conventionally done in medical science, but it's standard in social sciences, many branches, widely used in psychotherapy outcome research, it's what you do in clinical practice, it's what you do in real life. If you're down from the frozen north, you've never seen a banana, and you want to know which tastes best, yellow bananas or green bananas, they use a correlative approach randomized draw. You take a bite of a couple of yellow ones and a couple of green ones, and then unless you're pretty thick, you have a fair idea of what goes with what, right. It's the same kind of idea basically. It's also the approach used by many of the most influential workers in psychology, Freud, for example, dare I mention people like that, Freud, all doing -- they're all doing correlative one-on-one -- one by one detailed studies of individual cases, and that, of course, can lead to profound generalizations about psychology. The next one, to make it as rigorous as possible, we've tried to satisfy the -- the following requirements. It had to be prospective -- looking back at remarkable survivors because you don't have a denominator. You don't know how many people did something. If you think grapes cures someone and somebody -- somebody comes up and says I ate nothing but grapes for a month and -- and whoopie, I'm cured, you don't know how many people ate nothing but grapes and were not cured, you have to know that. So it

has to be prospective. Longitudinal, follow people for an extended period, characterize them repeatedly to see change. Using intervention, as I've said, to maximize change you need excellent medical documentation to control for individual differences in prognosis. And in the good psychological characterization, very comprehensive, and I'll come back to that. This is our experiment, small in number, reflecting on 22 people, 22 patients, metastatic cancer, my collaborators down the left. People were enrolled for a year of weekly group therapy. They all had medically certified and curable cancers, nearly all metastatic. To control for the medical status, when each person entered the trial, the charts were gone over by a panel of 14 oncologists, most of whom would then give a prediction of survival. So we can take a medium prediction of survival, taking into account the individual features of each person. We're grateful for my colleagues for helping with that. The intervention was this long term group therapy yearly -- in weekly meetings for a year, long contact, the principal therapist in this, and with a lot of training in self-help techniques, and a lot of work in the spiritual aspects of care. So we tried to cover the range. We tried to help people evolve, if you like, rather than support, it was an educational evolutionary approach on top of support. Data collection, extensive verbal data was taken at each meeting, and people did a lot of written homework, often amount to tens and hundreds of pages. And all of this stuff was -- was characterized by -- by putting it into a -- into dedicated software and doing qualitative analysis, using a ground process called dimensional analysis, which generated a lot of themes. An example would be application to self-help work. Another example would be the confidence that people could make a difference to the disease. These themes were not removed from the data, it's the essence of qualitative analysis. I don't think I have to predefine themes, you can find them out as you go along. And so now having done all that, the aim was to relate these themes to survival, and there's various ways to analyze the results, and much of it has been published, so I'm going to show you what's a visually simple way of analyzing. We -- we developed a complex theme, a very comprehensive theme called involvement in self-help. Here are some of the, not all, but some of the sub-themes. The amount of work done surely but also, more importantly, the dedication people showed or didn't show, reinforcing experiences that they had to keep them going, their perceived need ability to change - ----- outcomes expected, definition of goals, their ability, trait-like ability to act and change ---- a lot of people. So we -- we combined a number of our sub-themes into this comprehensive index. And then we could rank people, the 22 people could be ranked as high, medium, or low in their involvement in self-help. The high people were people who, and you've all seen such folks, who really got involved in helping themselves, and spent several hours a day, healing as the dominant thing in their lives, and dropped off -- resigned from work and so on in order to devote time, because they had an incurable prognosis, remember. At the low end were people who came along for the support and enjoyed that, but were pretty apathetic or dismissed all the possibility that they could actually influence the prognosis at all, and we've all seen those people, and that's perhaps the norm really in our present day culture. I can show the results in various ways ----- our survival curves for the high, medium, and low, and with a good -- quite a good degree of separation. Two of the people -- two of the women, and they were mostly women in the study, have had complete seven year remissions and are well and walking around, and they were both supposed to be dead in about a year. You would say that's not very impressive. We've all seen remarkable survivors. It becomes impressive when you take a sample prospectively and make the predictions. You don't expect two out of 20 to completely survive. And the next slide shows this in a slightly different form. This is published in Advances. If you look on the right-hand side, I'm looking at these three sub groups, high, medium, and low involvement, right, and looking at their

survival. The lows survived just over a year on average, the median actually. The high, the blue dot, survived an average just under three years, two, as I've said, are complete remissions, and the range is greater. And the intermediate, we have a bit of a dose response, and the people who did intermediate amount of work like they're intermittent or not sure, hot and cold about it, did an intermediate length of time. That turns out to be significant. Now, you might say, well, perhaps it's just a reflection of different medical status, so of course, the medical controls are important. On the left-hand side are the same three sub groups, the medium predictions for survival, and they were the same for the three sub groups. You might say, well, doctors are not very good at predicting, and we know that they're not in individual cases, so we did a control for that. Diamond is a group of deceased people we took from the records of similar prognoses. Those were the predictions in the left-hand panel, the right-hand panel are the actual survival and medians not too bad a correspondence between the two. There were no, I should say, no significant differences in the main prognostic factors and their age, quality of life, or the intake. And most important, I think, there was no significant difference in attendance between the three sub groups. It wasn't that people came in and then got sick and too sick to work, as you might think if you hadn't seen the phenomena, and that's why they didn't do much and didn't score high, that wasn't the reason. The people were well enough, all of them, to work for sometime. But they declared themselves within a month, they're going to work and they were keen, they would do it; if they were -- if they were not going to get on with the self-help work very much, then they wouldn't right from the start. The next one, just for fun to show something ----- from Dean Ornish's -- I think he's at the conference, from one of his studies on -- just to show that in his program, the people who inhaled most medium and least, very similar results, very similar numbers, showed corresponding degrees of difference in the -- in the enlargement of the luminal arterials, whatever it was, changes in the diameter of stenosis. I think -- I mean this is early days but I think it may turn out to be a general phenomena in health psychology, not just -- not just cancer, that as people get involved, I mean the actual nature of the involvement, it may not be the critical thing, within reason. But as people get more involved, they do better, and we've all seen that, and we need a lot of research to -- to prove it. I can't show you the -- I can't really do the qualitative discussion -- discussion about the qualities of these people in a short talk, but I just wanted to show you these pretty slides. This is, again, the ranking of people in involvement on the left, high, red, moderate and low, green, black is good, so the degree of involvement is the -- is the third last column, quality of experience, is the second last column, and survival duration is the -- is the last column on the right. So high involvement tended to go with good quality of experience, tended to go with long survival not invariably, you wouldn't expect it, but mostly. And I'm breaking that down in the next slide. If you look at the high's. Now, this is where it gets interesting when you do this kind of study of people, you get to know them intimately well. I mean I knew these people better than I know some members of my own family by the end of the year, I think, because they were very open about what was going on with them, it was great, very privileged really. The top four we're whole heartedly involved, they're sub clusters now, whole heartedly involved, healing was their life. The next three were conscientious about it, but they weren't totally whole heartedly, still led ordinary lives, as well, you know. And the next two were interesting, because they did a lot, but they had independent agendas, they were saying don't you tell me what to do, I've got this, this, and this, and I won't touch that, you know, we've all seen that. I'm trying to -- trying to get my paper published documenting all this, having a bit of trouble, but it will get out. The next -- the next slide, this is the bottom end. These are very different people. In the three, you have three sub groups, obviously, but at the bottom end, very

different people. We've got four people with difficult personal issues, low self esteem, it's just tough for them to hold themselves together, they can't do a lot of self-help work, they just haven't got the -- the extra energy for it, and we've all seen that, and it's not fair to expect such people to do much, I don't think. Then there are two people that skipped a call, one of them is a physician, one is a professor in the university. Such people are very hard to help, and not surprising, because their realistic world view has worked well for them and they are not about to change, so you can't do much for them except support them. And then there are two who are active rejecters, likewise. So -- and the next one I think is -- goes to the intermediate. They're people with problems to varying degrees. I'm aware that it just doesn't do justice to it to -- to talk about it here. The next spot is our web site. You can find the papers on that if you want. And also the references are given in the -- in the book. So I don't claim this one experiment is definitive, I'd be in trouble if I did, and rightly so. But I want to -- what I want to advocate is, we're at the point, and you'll see with Pam's very definitive experiment, we're at the point, I think, where we should consider doing things other than randomized trials in this field. Unfortunately, randomized trials have a very serious hold -- hold on the -- on the popular mind and on the founding bodies, and I consider them to be somehow better than exploratory work. I think that's going to be counter productive to put all our resources into that kind of work. I'm struck by the contrast in what we learned from the two different kinds of experiments. We are currently replicating this and finally got funding after six attempts from a national body to do it with 100 patients instead of 22. And in some ----- as you see for yourself, and I'll get off the podium, we're trying to define states of minds that are associated with living longer. I believe we need correlated designs which focus on individuals rather than group means. We need to incorporate a therapy, which hasn't been clearly recognized always in the past, focus on what people do. The therapy is just a scaffold. The therapy isn't what does it. A drug may do it, but the therapy doesn't do it. The therapy is a scaffold for the patient to do things. That's a very big difference in the whole nature of what's going on. We need to characterize people's psychology very closely, not rely on psychometric pencil and paper tests. Eventually we'll need to use -- come back again to the experimental design for randomized trials ideally using multiple interventions tailored to the individuals. Thank you.

DR. SAGAR: Thank you, Alastair. So now I'd like to introduce Dr. Pamela Goodwin.

DR. GOODWIN: Thank you. And I'd like to thank the organizers for having the -- having team Canada come down and talk to you. I am going to talk to you about one of those randomized trials that Alastair has just told you may not be the best way to approach this -- this area. I'm going to argue that it is one of the best ways. But you'll see from my conclusions that perhaps I have some agreement with Alastair regarding the need to refine the interventions before we go on to the next generation of randomized trials. So our study is called the Breast Expressive Support of Therapy Study, acronym BEST. I didn't choose that, but I wanted breast, breast randomized expressive support of therapy trial, but that was already taken. This is a Canadian study that was funded by the Medical Research Counsel of Canada and the Canadian Breast Cancer Research Initiative. And there were a large number of investigators across Canada involved in this study. It was multi-disciplinary. I'm a medical oncologist. I was the principal investigator. Mullen Lesh (phonetic) who's a psychiatrist, was the co-principal investigator. And at each center, we had a mixture of medical and psychological or psychosocial investigators that worked together to recruit patients and to deliver the intervention, and they are listed on this

slide. We were struck by David Spiegel's publication in 1989, suggesting that there was a survival benefit for support of expressive therapy. This survival benefit was seen in a randomized trial conducted in California in the 1970's that was designed to look at the impact of a specific therapy on psychosocial functioning. It demonstrated a beneficial impact on mood and on experience of suffering from pain, but -- but it was not designed to look at a survival effect. David retrospectively looked at survival about 10 years after the trial was completed and identified a significant prolongation in survival in women participating in the support group. But I think we need to recognize that numbers were small and that the survival benefit was really dependent on the long survival of three women in the intervention arm. There have been a number of publications since then. On this slide, I've -- I've tried to include the truly randomized interventions. I have missed one or two. But to make a long story short, there are a couple that have been positive, one in breast, one in melanoma, and one in GI cancer, and there have been some that have been negative. Our study isn't on this slide yet. We began this study in the early 1990's. Our objectives were in women with metastatic breast cancer to determine the effective weekly supportive expressive therapy on survival being our primary outcome that drove our sample size calculations. Psychosocial functioning measured using a battery of standardized psychosocial questionnaires, and I'm going to report on the POMS and a pain questionnaire today, and health related quality of life. We use the EORTC quality of life questionnaire. I'm not going to report on that today. We also stored blood for analysis of potential mediators if we happened to see a survival effect. Next slide. This is a scheme for the study. Potentially eligible women were referred to the study. In fact, we ultimately randomized just over eight percent of potentially eligible women at our participating centers. That is an excellent randomization rate. Published rates in the literature from medical studies range from three to 12 percent, so we did very well in terms of randomizing women. They had to have a life expectancy of at least three months; they had to speak English; they could not have CNS? metastases; they had to participate in a psychosocial screening questionnaire -- screening interview where they met with group leaders to rule out active depression untreated, and the reason for that was that at most of our centers, the people running the groups were also the people that provided psychosocial care to patients with cancer, and if they had a depression and we were potentially randomizing them to a control arm, we wanted the depression treated before we randomized them to a no treatment arm. They also ruled out or excluded patients with severe personality disorders. In fact, we only lost four or five patients at this step in the entire study, so this was not a major hurdle. The women also completed the psychosocial questionnaires prerandomization. They were randomized in a ratio of two to one to the group versus control. The reason for that was, we needed to have sufficient women to maintain active groups at centers across the country, so we -- we had a double randomization to the group intervention. It wasn't because we hypothesized a priority that the group was better. It did impact on our sample size, and we had to increase our sample size to account for the two to one randomization. Women were randomized either to the intervention or the control arm. I'll talk about them in a little bit more detail in a couple of minutes. But basically, it was group supportive expressive therapy in addition to all standard medical and psychological care versus standard medical and psychological care. Our primary outcome, as I've mentioned, was survival. Next slide. Randomization was performed centrally, it was stratified for center, a study site in visceral versus non-visceral disease. Next slide. Control arm, they received all of the usual care that was provided at the center including usual psychosocial care, and they also received regular educational packages. Next slide from us. Intervention arm, the very same, and in addition to that, they were under -- they were invited to participate in weekly supportive

expressive therapy. Next slide. Our supportive expressive therapy was described by David Spiegel. We rigorously replicated his intervention. We used his treatment manual, he trained all of our leaders, and he met, he or Catherine Clausen, one of his collaborators, met with our leaders every 9 to 12 months to ensure that the intervention was delivered properly. And he has stated repeatedly in public that he believes we rigorously replicated his intervention. Basically, the -- and I'm not going to go into the details of the intervention, because I think most of you know about them, but I will try to just hit some of the main areas. I was one of the group leaders for a period of about three years during the intervention. Mullen Lesh and I lead a group together. So I'm pretty familiar with the intervention. They were weekly 90 minute meetings for at least a year. They involved six to ten women and two leaders. At least one leader of each pair had to be a woman. The focus was to foster support and social integration, to encourage full emotional expressiveness, to enhance coping strategies. There was a self-hypnosis relaxation exercise at the end of each meeting and women were provided with a tape that they could practice -- use to practice at home. And there were a number of topic categories that we wanted to be addressed over the course of the intervention, obviously not every week, but they included things like life values, and property, and principals, scoping skills, doctor/patient relationship, dealing with death and dying. We put a lot of effort into standardizing the intervention. Next slide. And these next three slides are from Mullen Lesh, my co-PI. The training was manual based and involved workshops every six to nine months. There was also a video tape review once per month, it was randomly selected at the end of each session or the end of sessions by opening an envelope, one a month had an X in it and that was the tape that was sent in. That was reviewed centrally by Mullen. Next. The tape was evaluated for adherence to the manual based intervention. We looked for the presence of essential factors, the absence of undesirable factors. We looked over time, topic, categories were all addressed. Mullen assessed competence in terms of general competence and context dependent competence. And leaders were provided with written feedback of these monthly tapes, as well as telephone and conference calls when necessary. They were also given feedback in workshops where we reviewed some of the tapes as a group. Next. Group members also completed two process questionnaires, the group climate questionnaire and the group relationship questionnaire during the week that the video tape was reviewed, and group leaders completed a general and specific therapist evaluation form. We have not yet completed analysis of these questionnaires. They say if you spend ten years doing a study, you'll spend the next ten years analyzing it and I think that's right. Next. Our group leaders, they were -- they had a range of professional backgrounds, psychologists, psychiatrists, social workers, nurse, I was the one medical oncologist. I had done group work before in primary breast cancer, so I had had some experience leading groups before I started this. Average 12 years of professional practice and average nine years of psychooncology experience. Next. Ten were female, seven were male, and most of us were in our 40's. Next. And again, these were very experienced group leaders. They had all had professional experience with life threatening illness, they had prior experience with cancer patients that was extensive, prior -- extensive experience with breast cancer patients. Next. And here they are with David Spiegel sitting in the middle of the front row at one of our group leader's workshops. A pretty happy looking crowd there. That was just a couple of years into the study. Next. Yeah, the results hadn't come out yet. Anyway, we began the study in the early '90's. It took us about a year to get our team together. We were actually on our first application, which was I -- I think really surprising. It then took us a year and a half to get ethics at all the participating centers. Some centers felt that the benefits of group therapy were so clear, it was unethical to randomize your control group. Other centers felt that

the benefits or the -- the detrimental effects of group therapy were so clear, it was unethical to randomize to a group. And we couldn't start anywhere until we had ethics everywhere, so that was the biggest challenge in the early years. As you can see here, recruitment went pretty smoothly. We did add in a couple of centers later on in the study to boost recruitment, and we were constantly selling the studies, me to my medical oncology colleagues and the psychosocial investigators to their psychosocial colleagues. But working together, we did randomize over 230 women. Next. And what -- who were these women that we randomized? What I'm showing you here is some characteristics of the women at randomization and then looking backwards to their breast cancer diagnosis, some characteristics years earlier. All of the women had metastatic breast cancer at the time of randomization, that was a criterion to get into the study. So they were around 50 years of age, about five years post-diagnosis, about a year and a half after first development of mets. They tended to have good performance status. In fact, they couldn't have ecog three or four, in other words, they had to be fully mobile to come -- to be randomized, because they had to be well enough to attend the group. Just under half had visceral involvement by metastases, and about 40 percent were receiving chemotherapy and hormone therapy at the time of randomization. There were some minor -- and all of these factors were balanced between the two groups. There were some minor imbalances in factors earlier on, at the time of diagnosis. We looked at about 20 different factors. I'm showing you the four that were imbalanced, and three of them are highly correlated. The women in the intervention group were a little bit younger, they were two years younger, but because the -- the group sizes are so big, that was a significant difference, and they were a little bit more likely to be premenopausal. They were also a little bit more likely to be node positive, okay, and that combined with age led to a higher likelihood of adjuvant chemotherapy being administered, okay. All of those factors are prognostically important at the time of diagnosis. But once a woman has developed metastasizes, in other words, in the women that we enrolled in our study, they're no longer prognostically important in the literature or in our patient group, so these imbalances were interesting, but they didn't impact on our outcome. Progesterone receptor was a little bit different. Our intervention group was a little bit more likely to be progesterone receptor positive. They should have lived longer. The impact of that was that the intervention group should have lived longer, okay. And just remember that when I show you the curve. Next slide. There was no difference in time from diagnosis to first mets, first mets to randomization or diagnosis to randomization. I'm showing you these numbers because these were imbalanced in David Spiegel's original study and he was criticized for this. Ours were balanced. Next slide. For the entire study group here, there were no significant differences between the arms. But most of them were living with others, usually with family members. Most of them had more than two close relatives they could rely on for assistance and support. Most of them had more than two close they could rely on for assistance and support. Almost all of them had the presence of a special person they could turn to for help. And 75 percent of them were either very or completely satisfied with their relationships. This was a very highly functioning group that had a lot of social support when they entered the study. Next slide. What about compliance with our intervention? A hundred and fifty-eight women were randomized to the intervention, 24 percent of them died during the first year. We asked women to participate for one year and told them they could remain in the group longer if they felt it was helpful. Nineteen percent dropped out. The median time -- meantime to drop out was 3.5 months. That's actually a pretty good drop-out rate for a psychological intervention. And our group attendance was about two-thirds of sessions were attended. Given that these women were medically ill and were dying, we feel that that's also a very good number. Next slide. Did women

in the control group or the intervention group receive psychosocial intervention off study, okay. Well, pre-randomization, about a third of the women in each group, had participated in either a support, sorry, in a support group of some sort, okay. Post-randomization, about eight percent of women in the intervention group and ten percent of women in the control group participated in a support group off study. Usually these were church groups, that was the commonest type of group. And in addition, about a third of intervention and control subjects, no difference between the two, had at least one session of individual therapy after randomization. So there were no differences in co-intervention of psychological interventions between the two groups. Next. Well, what about our intervention and how did it impact on mood? I'm going to show you a couple of psychological outcomes before we move to survival. Well, this is the POMS, it's a -- is everyone familiar with the POMS, self-administered questionnaire measuring mood? It's got six sub scales and a total mood disturbance scale. And these are the baseline scores. And what we saw was, there was a tendency for higher -- for the intervention group to be a little bit more depressed, a little bit more tense, and a little bit more angry at randomization than the control group. You look at these scores and you say, okay, nine versus twelve, is that clinically significant? Well, it might be, but all of these scores are quite low, and the difference between the two groups is not statistically significant. We had originally analyzed this assuming a normal distribution, and the P values were slightly lower, we were getting some .04's, .05's, the distributions weren't normal, and we -- when we analyzed the data using nonparametric approach, as we got slightly higher P values. I'm not sure it makes much -- much difference, but to us it was saying there might have been a tendency for slightly greater distress in the intervention group than the control group. We've analyzed all of our other psychological questionnaires including the impact of events, the psychosocial adjustment to illness scale, the quality of life questionnaires, and we saw no other baseline imbalances. We've looked at a total of 50 different psychological factors. The only three that came close to being significant were in the POMS, okay. But I'm -- I'm saying this very honestly because it impacted on our analysis of results. Next. We looked at change over the course of a year, and what we see is that there is a greater improvement in the intervention group than in the control group, and negative change means an improvement in mood in this -- using this particular questionnaire. And these differences between the intervention and control group were significant for total mood disturbance, depression, anxiety, anger, and confusion. Because we had seen those baseline imbalances that were almost significant, we thought it would be important to control for those baseline imbalances and to look at whether they impacted on the beneficial effect of the intervention. So what we did was an analysis of co-variance, where we included an interaction term. And what that interaction term allowed us to do was to ascertain whether the intervention worked differently in distressed and non-distressed women, and we found that, yes, indeed, it did, that the -- there was a significant interaction between baseline scores and -- and effect of the intervention for total mood disturbance, depression, anxiety, anger, and confusion. And if we could have the next slide. I'm showing you this, the impact of this intervention in a graphical form for total mood disturbance. The others follow the same pattern. And what we can see, on the left-hand side of the slide is women who have low baseline distress, and we define this as below the median. We see no difference in change over a year in the intervention group versus the control group. Those curves, the bottom curve under low baseline distress is the -- is the control and curve is the intervention. When we go to women that have high baseline distress, we see a very different pattern. And what we see is a significant reduction in distress in the intervention group, but not in the control group. And this difference is highly statistically

significant. Okay. So what this is telling us is, the intervention helped mood overall, but the effect was present when we analyzed it according to baseline distress. The effect was present in women who were initially distressed, not in those who weren't distressed. Next slide. Now that we've been through that, I can go through the next one easily or quickly. Similarly for pain, we -- for pain we didn't see a difference in baseline score. We had experience of pain and experience of suffering and hurt. The women filled out 10 centimeter scales. Next. We looked at change over the course of a year. And in this particular scenario, and a positive score means greater pain, so that's a worse outcome. And what we see is that for the intervention group, there is less worsening of pain, experience of pain, than for the control group. And we're -- we tested for an interaction because we had seen one for the mood variable. So even though we didn't see a baseline imbalance, we thought we should look for an interaction -- an interaction here, and again we did, and we -- if we could see the next slide. We're seeing the same pattern. Women that were experiencing pain had a reduction in pain if they were in the intervention group, but an increase in pain if they were in the control group. Okay. If they weren't experiencing pain at the beginning, there was no difference between the two arms. So once again, we're seeing the intervention is impacting on women who are experiencing pain to help them with their pain. Next slide. Well, what about the effect of the intervention on survival? You know, we -- the data I've shown you so far, I think, are very positive outcomes. The intervention is benefiting mood and pain control. What about survival? Next slide. We saw no effect of the intervention on survival. Okay. The top curve here is control, the bottom curve is intervention. P value is .72. If we could go to the next one. We did a multi-variate model where we included all of the potential confounders, and we still did not have a significant effect of the intervention on survival. In fact, the hazard ratio is above one. It's not significantly above one, but it is above one, consistent with a slight trend towards a worse survival in the intervention group, not significant, but we're not seeing even a trend in the direction we expected. We -- what I'm showing you here is -- is a multivariate analysis that included a number of biological factors. We've now done multivariate analysis that included study center, marital status, and total mood disturbance at the time of study entry. None of them is significantly related to survival, none of them changes this effect, this result. So we are not seeing an effect of the intervention on survival regardless of how we look for it. We can stand on our heads, we still don't see it. Next. Did we miss one? Well, Alastair talked about a Type II error. Well, I don't really think we had a Type II error. We had 85 percent power to identify the effect we wanted to identify at the beginning of the study. We had 99 percent power to rule out the effect that David Spiegel saw. I don't think we missed the survival effect because our study was too small. I think our intervention was delivered successfully. We have video tape confirmation of that. We also are seeing a psychological benefit, so I think that tells us the intervention was delivered appropriately. So I don't think we missed the survival benefit. Next. So where are we? Well, I think the -- we can conclude that the addition of supportive expressive therapy to standard care, I guess I should say in the Canadian setting because this is the Canadian team, in metastatic breast cancer, does not result in prolonged survival. It does improve psychological functioning in women who are experiencing psychological distress, and it does improve pain in women who are experiencing pain. Next. Future research, I believe, should focus on the identification of optimal approaches to reducing psychological distress in women with metastatic breast cancer. Next. And some of the questions that I think need to be answered are who benefits and who does not, do all women benefit, is it only distressed women, how long should the intervention be, and what should the intervention be? We've shown a benefit for supportive expressive therapy. I'm very happy with that. But I

also recognize that this is a very difficult therapy for therapists to deliver, it's very labor intensive, it requires a certain amount of skill and supervision, and it may be that there are other easier or more readily available or shorter interventions that could obtain the same benefit. When it comes to the issue, if I could just editorialize for one minute; can I have one more minute? When it comes to the issue that Alastair was raising about how should we address survival effects, we agree and we disagree. I agree with Alastair that the currently available interventions do not seem to impact on survival. I agree that if we want to do future research, looking at the impacts of these interventions on survival in metastatic breast cancer, we need to look at other interventions. And perhaps one of the ways to identify what interventions we should study are correlative studies. I'm not sure, it may be that we can do some randomized trials, looking for changes in intermediate outcomes, like physiological parameters or psychological factors. But my question and my challenge to all of you is whether or not this is the appropriate setting to do these interventions in. Is it reasonable to think that a psychological intervention is going to impact survival in metastatic breast cancer, and if it is, is it reasonable to expect to see that with some of the intervention studies we're doing? This is one of the most difficult types of cancer to treat. There are very few drugs that will impact survival in metastatic breast cancer, and they've only been drugs that have been introduced in the last five years, and they impact survival by maybe four weeks, three weeks, two weeks, they don't have a big impact. If we use this setting to determine whether drugs were effective in -- in -- in cancer, we would have thrown out almost all of the currently available drugs. They would never have gotten to the situation where they've actually ultimately been shown to be effective. Metastatic breast cancer is a cancer that's highly resistant -- resistant to treatment. I don't want to discourage people because we have treatments that will control the disease, we have treatments that will improve symptoms, but it is one of the more difficult cancers to treat. It's one of the cancers that has accumulated the greatest amount of DNA damage, making it highly resistant to treatment. And I think that if we're going to look at the impact of psychological interventions on cancer outcomes, on biological outcomes, we should focus on a different stage of disease and possibly a different type of cancer, so that we can have the greatest possibility of impacting survival. And once that's demonstrated with a specific intervention, then maybe we could move back to the really challenging scenario of metastatic breast cancer. There's only one that's more challenging, that's metastatic lung cancer. So that's my two cents worth. Thank you.

DR. SAGAR: Thank you for a very thorough presentation. And it's really exciting to see that you can apply rigorous methodology to a subject which at first appears to be more than challenging, to be able to do randomized control trials on. So I'd like to now introduce Julia Rowland, who will make some comments.

DR. ROWLAND: I would like to thank the organizers for the opportunity to come and be a commentator this morning on these wonderful and very important presentations. And I want to take this opportunity to talk a little about the history of why we're even here. And to do that, because so much of the work that's gone on, the work that Pam has done and that Alastair has done, has really been built on this very important study that David Spiegel and colleagues reported on in 1989. I just wanted to talk about the history of that and sort of frame that for us. Because when that study was actually conducted, David and colleagues, this was back in the mid-1970's into the late 1970's, the treatment for breast cancer, and I think Pam alluded to this in the end of her presentation, the treatment for breast cancer was very different than it was today.

The prognosis for women with metastatic disease was very grim, the survival time on average was about eighteen months, there were very few resources, and then some of you have been in this field long enough to realize there were very few choices for women. All of these women underwent mastectomy, we didn't have lumpectomy, there were very few decision points along the trajectory, very few treatment regimens that were effective for women with these advanced diseases, it was stigmatized, you certainly didn't talk about it. 1976 was when Betty Ford first came out and talked about having nodal involvement in her cancer. Most women at that point in time didn't even know about nodes, they were not told about nodes. The surgeon went in, took the tumor out and said go on, live your life, there was no follow-up, there was no emphasis unless you had nodal involvement, and even those women weren't told about it. So the design that David and colleagues put together was actually a very compassionate one. And their intent in putting it together was not to prolong life, but rather to address the quality of life issues, the health related quality of life of these women, to reduce their suffering, and it was very effective in doing that. Their data, and they published many papers, did just what they set out to do. It helped women suffer less, it helped women feel that they could cope better, they were better able to negotiate their medical visits when compared to standard care, did what they wanted to do, end of story, they walked on, onto other things, that was it, except that the field moved beyond them. Studies began to come out and there was sort of a lay sense that your mind could alter your cancer outcome. And it was actually in reaction to some of the public experience that if you just had the right thoughts, you could beat your cancer, you could think it away. David went back to look at the actual data on this intervention, because he said actually I have a study I can show you, we did this very wonderful intervention, we improved quality of life, but you can't prolong survival, and lo and behold, to his shock, his data would have suggested, and when you look at his data, and Pam showed it to you, if you were to show that to a medical audience and not tell them what the intervention was, it looks like taxotere or herceptin, it's that kind of a dramatic survival curve that looks like a treatment effect in here, and the publication of that data turned our world, the psychooncology world, upside down, because it changed our paradigm. I think many of us were traveling in the area that we felt we could improve the quality of life of individuals, but never had any hopes that what we were doing would necessarily be life prolonging, that our goal really needed to be quality of life. And the reason I want to keep coming back to that is because I think the temptation in listening to the presentation of this BEST study, and you think the best care, the best care, you would think that these -- this should be the best. The fact that there is no survival benefit in this study, I'm concerned that people are going to think, well, we should stop looking at this, we shouldn't be doing these interventions for some reason, I don't want to throw the baby out with the bath water, it's very important, because what we can do, though, is significantly alter quality of life of individuals. And it's going to be important for us to keep that on the horizon because it's going to have funding imperative for us if the -- if the feeling in the -- in the general public is that if we can't prolong survival, why are we doing this at all, that it's not beneficial. And I think that that is a point that we have to keep in mind. Another argument that you can say in looking at Pam's data in particular is, well, gee, you know, one of the issues is that there's so much more for these women, there's all kinds of support, she acknowledged that these women felt very well supported by their community. Breast cancer, particularly, is out of the closet, so to speak. There are all kinds of resources for women who are diagnosed today. Very -- a third of these women avail themselves professionally led groups. We're not even counting peer led groups. We're now the ramp and access that women have on the internet, in their community, just generally given in the clinical oncology setting, very

different than back in the late 1970's. There are many more treatment options, there are many more supportive care products. We now have ----- for the boney metastophy (phonetic) we now have blood products to reduce the anemias that go with treatment, we have better radiation treatments, et cetera, so we can support women a great deal longer. In fact, this is one of the ironies with David Spiegel's replication study, his has not matured as quickly as Pam's, because the women aren't dying fast enough, the high end problem, I admit, but he has to wait for enough women to die before he can actually break the code in here to see whether or not this is having an effect, because the climate has changed, the medical climate has changed, the psychosocial climate has changed, and that really underscores what Pam ended with with saying is this the right paradon. We probably need to be shifting into an area where there are fewer resources, advanced colon cancer, large numbers, lung cancer of any kind probably would qualify, recurrent ovarian cancer, maybe these are the areas where we might effectuate change. And that then brings me to what Alastair was saying is I don't see that it's either or, that we need to have either intervention or ----- we need to actually be combining the two, probably also in randomized trials, because I think Pam can go back and look at some of her data, and they have very explicit data on some of these video tapes, et cetera, and certainly David Spiegel has a lot of video taping in here. You can begin to look at individual characteristics. They can actually almost thumb print the women's participation in here with the analytic content of what goes on in those sessions, so you can look at change that's occurring across the course of the intervention. Who benefits most? I mean these are the critical questions that we are faced with now. Who should have what kind of care, when in the course of their illness trajectory, delivered by whom, paid by for whomever, and are there multiple models to this, what is the most efficient way, can we afford to deliver a year of intervention care? I would say in the current medical climate, forget it. They don't care -- even if you had prolonged survival, my fantasy is the insurance companies say I'm not going to go there, let the women die, it's cheaper for us, a very hostile comment, but it's the kind of thing we worry about in here in looking at how can we do this and how can it be practicable. We know, again, from these studies that have been well modeled, an important feature for us is making them replicable. When we look at ----- therapy, one of the challenges that's always been on the table is, can these be reproducible, is it just a provider phenomenon, can we take this, manualize it, have good quality assurance, show that it's replicable, and deliver it in other populations, and that is going to be a critical hurdle for us as we go forward. Another is, and I think Alastair illuminated this, we don't really have good instruments to look at this. You have to remember, in the psychooncology field, we've been looking for pathology. We've used psychiatric scales to define and describe the populations that we look at, looking for deficits, dysfunction, disability. We have very few scales and very little emphasis until recently on resilience, positive coping, adaptive mechanism, life view changes, spiritual concerns in here that we're just beginning to delineate and define so that when we say we want to do an intervention that's going to change that, the intermediate marker may be change in that capacity, change in ability to express emotion, change in world view, change in resilience, in sense of coping, active participation and care. We need measures that allow us to serve as the intermediate markers to say are we actually doing what we set out to do with our interventions, to be able to say that that's what is working. And then -- so ultimately, we're going to need to tie those to the biologic market. Maybe that's a PSA level, maybe it's natural killer cell or immune functioning in some way, to find out what's going on in the black box that we may be changing with these external factors in here. The final thing I wanted to conclude with is, and I don't know how many of you are familiar with the fact or realize before you came to these meetings that we have an office of

cancer survivorship at the National Cancer Institute, we have a growing research portfolio, and our portfolio analysis that we conducted for fiscal year 2000 in which we looked at grants, not just within the cancer institute, but across all of NIH, because though we co-fund David Spiegel's study, the primary funder for that study is the National Institute of Mental Health, which I will tell you historically going forward is not going to be funding a lot more cancer because they can't afford to, it's going to come to us. But if we look at that portfolio, NIH and the Department of Defense, because as many of you know, they are big time in breast cancer research and in a growing presence in prostate and ovarian cancer, hopefully into the future, but when we look at that portfolio analysis and we have 134 grants in that, about 50 percent of the grants in that survivorship area studies picking up people anytime from diagnosis, post-treatment. Half of those grants are intervention studies. So we know we're out there doing interventions. The problem with our science is that everybody keeps reinventing the wheel. Pam and David is -- are actually examples of the first time when someone has actually taken a study that showed efficacy and tried to replicate it. We have a terrible track record of doing that, unlike our medical colleagues who find their drug treatment, do it in a phase two clinical trial, and then say it works, go to their colleagues, and take it to a phase three or phase four, getting it out into the community, trying it in larger, more generalizable populations, we do not do that in the psychosocial field, in the mental health arena as far as cancer is concerned. It is a major hurdle for us. We need to begin looking at what are the interventions that work, trying these in larger populations, seeing if we can change who delivers those. The only other study that I can say tried something like this is, you heard reference ----- study, this is a study conducted back at UCLA looking at melanoma patients, six week intervention, very simple components, manualized, actually it was manualized in breast -- published manuals in breast cancer, not in melanoma, interestingly. Four components to it was education about the disease, progressive muscle relaxation, coping strategies in here, and just general support, very simple intervention, and they showed significant differences of six year follow-up in rates of death from melanoma in this early stage, surgery only melanoma, population men and women. His wife, Nancy actually tailored that intervention and redid it just so a nurse could deliver it. Now, I don't know that she ever looked at survival outcomes, but she certainly could show that the coping and the psychosocial benefits could be delivered in a nursing format, a rare instance where we've taken an effective study or an effective intervention and tried it in different populations. And that going forward is going to be one of our biggest hurdles, is trying, again, to get back to who needs what, when, where, and the course of care, trying different strategies, and finding ways that we can deliver this out into the community. Thank you. DR. SAGAR: Thank you. We have about 20 minutes for questions

SPEAKER: -- Goodwin. Doctor Cunningham, you compare -- your control group, when you compared high, medium, and low adherence groups, your control group was deceased patients in the -- in the -- that was the way you described it, I believe, in the chart you showed, and I'm wondering if that's a fair comparison and whether a fairer comparison would have been a group that had received some --

DR. CUNNINGHAM: No, sir, there was no control group, and I'm -- I'm sorry if I didn't explain it well enough. This is a correlated study where every patient is compared with every other one.

SPEAKER: Okay.

SPEAKER: And Dr. Goodwin, I'm just curious, I couldn't tell from the graph if there were outliers in the population of women who received the intervention, who -- who one might argue did, in fact, receive a survival advantage from the intervention.

DR. GOODWIN: We have some long term survivors in both the intervention and control arms. The only way we can conclude whether the intervention impacted on survival is by comparing the two arms in their totality. There's always a broad spread or a range of -- of survivor links in -- in women with metastatic breast cancer.

SPEAKER: Hi, I'm another Canadian. My question deals with group therapy versus individual therapy. And I've always -- often wondered about this. There's a school of thought that says a cancer patient or other people who are terminal or degenerate diseases should perhaps even reject death, not go to funerals, not to associate with people in terminal stages because it gives them the idea that they're supposed to die, that this is the next thing. So what I'm wondering is, when you have people within a group, in a support group or -- of any kind and you have individuals of that group dying, that has to have an effect on the rest of the group. Has anyone looked at that? Has that been a variable you looked at in your own studies or anywhere else?

DR. GOODWIN: It's -- one of the things that we've captured but haven't yet analyzed, we have the group process measures which are -- can be linked to death of a group member, and one of the things that we want to look at is whether engagement with the group process changes when a group member dies. I think that -- someone asked us about outliers already when it related to survival. I -- I think that when it relates to this, I think there's going to be variable responses. I think just anecdotally, as we watch groups across the country, there were many women who, in the long term, were enriched by the death of co- members. They intended to detoxify death. That helped them give -- introduce more meaning into their lives, the survivors, and it -- it helped increase group cohesion. But at the same time, there were women who, despite being prepared for the deaths and receive support from other group members and the group leaders, dropped out and didn't come back. So I think that the -- the responses are somewhat individual. And what we're going to try and do is -- is look at whether there was a preponderance of response and -- and whether we can predict who might have had a beneficial -- had a good response and who might have had a bad response. So that's the type of thing that we're probably going to be looking at; we haven't had a chance to look at it yet.

DR. SAGAR: Very briefly, I think it's a clinical issue. I take it as ----- that working with people that are likely to die. One of the basic things you do is help them address the fact that they -- they probably will die. It's got to be integrated just as it does in the lives of any human being. Okay. That's the kind of baseline ----- and I'm sure it is in the supportive expressive groups, too.

MR. STALLBACK: I'm Leo Stallback from the Boston area. I would like to make a comment and then ask the panelists a question that I think is -- is a difficult one. First of all, in terms of what Julia said in regards to Spiegel's study, if you look at the fact that the survival in that group was actually pretty poor in terms of the first part of the study, the median survival was around 12 months, and I think that that indicated that there was a selection by us -- a negative selection by us. I think that in those days, people often were sent to essentially go home and die when they

were doing poorly, and here they -- there was a means of getting somebody involved in some kind of a project. And I think that -- that -- I would take issue with looking at those curves if you are a medical oncologist and saying that this is, you know, a sign of a good drug, let's say, because most of the time we look at median survival, and the median survival was -- was the same for the two groups, and so what you had was a tail of a curve effect. And Bernie Fox actually showed that both groups did worse than the ----- survival data, in other words, the national study. The question that I have is, if you're dealing with a situation where motivation is essential, how are you going to select patients who are motivated to participate in the study and get those patients randomized? The -- there you have a selection criteria which is on the other side and you -- I think it's a confounder, it's a -- it makes it difficult to do the studies, and I wonder how we can do control studies in a situation where the motivation of the patient seems to be central.

DR. GOODWIN: The issue you're raising addresses what's called the external validity or the generalizeability (?) of the study. It -- it doesn't impact on whether the results of the study are valid, it impacts on to whom the results of the study apply. In our setting, we clearly had to have women that were willing to participate in a group, yet also willing to be randomized. And we did have some women who did not participate because either they definitely wanted to be in a group or they definitely didn't want to be in a group. But those were not common reasons for declining the study. The common reasons were that they didn't want to set aside time every week, they -- they didn't want to -- to travel, if it was closer to home, they would be happy to do it, things like that. But something specifically relating to the group being in it or not was not a major factor. Now, this was mainly, in the early to mid '90's, I don't know if that would be the same today. I think in Toronto we now have so many groups off-study that I think most women with breast cancer, at some point, participates in a group.

DR. ROWLAND: That was actually one of the earlier problems that Dave Spiegel had in -- in running the ----- you know, here it is California and we all think, well, on the East Coast you can do the study, but in California everybody -- the drop-in effect is really a problem in here, it's controlling for that and having women say they -- they didn't want to be randomized, they wanted to be randomized into the intervention group, so that is -- that is a challenge. Leo, in response to you, I think one of the things we can think about and design in here, and there's certainly been investigators who have thought about this is, you can have people choose. You could have a randomized arm that -- you have two -- let's say you have two interventions, one is going to be a supportive expressive therapy and the other one is going to be an educational group, I'm just making these up. And you can have people choose which arm they want to go into in one group and the others are just randomized to it and answer that question. And I think all of our belief is once we start delivering this in the community, of course, motivation and choice and investment in something makes a big difference as opposed to you're being assigned to it. From a strictly research prospective, the randomized clinical trial remains, whether we like it or not, our goal standard.

DR. GOODWIN: Let me stir up one more issue. Many people view our results as negative results. But I'm not sure we would ever be able to do a control randomized study again in Canada because we've shown a beneficial effect on mood and pain control. So I think our results are positive, they're just positive in a way that perhaps we didn't -- well, we -- we figured we'd see

this effect, but we hope to see another effect, as well. So I think the -- the social situation, the ethical situation changes over time, and I think we're going to have to respond to that as we -- as we design most -----

DR. SAGAR: Now, it's effect another reason for thinking of other designs other than randomized trials, because often you can't do them. I recall the smoking situation, smoke and lung cancer. That's been established entirely by correlation. You can't do a randomized trial there, but nobody now doubts, that's my opinion causes lung cancer. It is more difficult and you have to control other factors and you have to let it emerge with a number of replicative studies, but it can be done.

SPEAKER: Pamela, what about applying this methodology in an agovent context, where you would expect physiologically there might be a better outcome?

DR. GOODWIN: I think in breast cancer that's a logical thing to do, and David Spiegel's group is doing it. I would also suggest that perhaps it might be logical to do it in illnesses where immune factors are probably more important than they are in breast cancer, melanoma, I'm amazed no one has replicated that nor tried to, I'm truly amazed.

DR. ROWLAND: It couldn't get funded.

DR. SAGAR: I would agree with that. I think there are many conditions that are better than metastatic cancer. And there are two studies at least going on around the world with ----- cancer. But the problem, as we all know here is, you need huge numbers to get -- to -- to determine a small effect, because otherwise people don't die, so your survival now is complicated.

DR. GOODWIN: It's funny, when I started this work, I guess I was hopeful that we would see a survival effect, I guess that's why I put 10 years of my life into it. But I -- I must -- I have to challenge you a little bit, because I'm surprised at the continuing, I don't know, desire or -- or, I don't know what the word is, want to see a survival effect for these interventions. There is nothing wrong with a study that shows that you've made women live better, you've made them control their pain better. I mean these are very positive outcomes. We often design drug studies trying to show we're improving quality of life or reducing toxicity. These are very positive outcomes, and I guess, Julia, you mentioned, I think, throwing the baby out with the bath water, don't throw the baby out with the bath water by focusing only on survival effects. There are many other beneficial effects, that I think we need to -- to value -----

DR. SAGAR: Thank you very much. Particularly thank you to the audience for some fascinating questions, and thank you to our speakers. Thank you.

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