Clearing the Fog: Understanding and Managing “Chemobrain”
Pamela Joyce Shapiro, PhD

LORI ATKINSON: My name is Lori Atkinson. I’m the affiliate development director with Young Survival Coalition and a 13-year survivor. I’ve been coming here for quite a few years and am excited to hear what Dr. Shapiro has to say today.

I want to just tell you how we’re going to run things and a few announcements before we get started. I want to remind everybody that this is audio taped, so when we do go through any questions, we want you to talk into the mic, which we’ll put back on the stand there. Hold questions to the end if possible, unless there’s just some misunderstanding and you want to ask the doctor during the presentation. That’s fine. Stay general on topic. Remember, we have a big audience that’s listening, too, so ... keep your questions open for everyone who listens.

I want to also remind you that we are doing the picture right after this session. ... We’re going to do that right after for the survivors.

I’m excited to introduce Dr. Pamela Shapiro. She’s a cognitive psychologist and assistant research professor at Fox Chase Cancer Center in Philadelphia. She received her PhD from the brain behavior and cognitive program at Temple University and completed post-doctoral training in behavioral oncology at the University of Pennsylvania School of Medicine and Abramson Cancer Center.

Dr. Shapiro’s research focuses on cancer-related cognitive change and the impact of cognitive loss on quality of life. Her research has been funded by the Department of Defense and the National Cancer Institute. She has presented numerous papers at national scientific meetings and frequently speaks at community-based cancer support groups. She served on the expert panel for perceived cognitive function and as a representative to the Alliance for Quality Psychosocial Cancer Care and the LIVESTRONG Young Adult Alliance Task Force. Welcome.

PAMELA JOYCE SHAPIRO, PhD: Thank you. I’m very happy to be here. I want to just amend that slightly. I was research assistant professor at Fox Chase when I was invited to do this. I am now an adjunct assistant professor at Fox Chase, so just in the point of accuracy, so they don’t think that I’m saying something I’m not. (Laughter)

I’m also a cancer survivor, not breast cancer but non-Hodgkin lymphoma, and this January marked 20 years. (Applause) However, it is 15 years since my diagnosis. I was accurately diagnosed in 1992, but they forgot to tell me until 1997. So, whatever. But in some ways it was a good thing because I didn’t have any treatment for those years and maybe chemobrain was delayed a little bit.

I did 11 months of chemo, and I’m telling you that because that’s how I got involved in this area of research. Before this, I did creativity research. But I noticed that I had difficulty remembering words and processing information, so I changed over to this field. I tell you this because all this time later, I am extremely nervous about presenting because I’m always afraid that I’m going to forget and that I’m not going to be able to find the words to say what I want to say. I’m in a group that I’m sure will understand that (laughter), and if I backtrack or go through my notes, you’ll forgive me.

Before I start, I want to do a little something with you. People usually come to these groups with someone they know or alone. If you’re with someone you know, you’re sitting next to them, but you don’t reach across the aisle and know people on the other side. What I’d like to do is
have everyone who is sitting in an end seat, middle aisle, reach over and introduce yourself to the person opposite you on the other end of the aisle. Just those people. You’re lucky. You got the hot seats. Exchange names.

You can all talk later, but we need to start the presentation now. I’ll explain to you why I do this. I’m going to return to it later. If I forget, someone from the audience will remind me: “Hey, you had people introduce themselves. Why?”

This was written by someone at The Wellness Community [now Cancer Support Community] in 1998. Back in 1998, we didn’t know a lot about chemobrain. It wasn’t a very common term. I’m going to read it:

“This morning I took my 13-year-old son to the doctor for his back-to-school checkup. The office is 10 minutes from my home. We’ve been there many times before. We arrive on time, have a routine visit and head for home.

“I pull out of the parking lot and head down the road. Things look familiar, as they should, and I make my turn, as I should. Only something’s not right. I’m on a street I don’t know, or at least think I don’t know. I backtrack and try again, then again, and yet again. My son looks at me strangely and asks, ‘Mom, are you all right?’

“I can feel the tears coming, my body tensing, confusion and frustration growing. I can’t be more than five minutes away from home, just a few blocks from our house, but I can’t find my way home.”

Now, complaints like these are very common among cancer patients — not just breast cancer patients, but breast cancer patients happen to be the most vocal group, so they’ve been studied the most. (Laughter) In fact, if you Google the terms “chemobrain” and “chemo fog,” you’ll get about 800,000 hits, but back in ’98 you didn’t do that. So, we’ve come a long way, but still, it’s a very young science and there’s a lot that we don’t know.

These are some examples of cognitive failure events, which are basically lapses in everyday cognitive function, things that happen to all of us. These were taken from a study I did at Fox Chase. It was a daily diary study. We only asked women who were diagnosed with breast cancer to keep a journal and write down any cognitive difficulties they had, and they did this on a daily basis. These are just a few of the examples:

“This afternoon I was driving to the plastic surgeon for my last visit. I noticed that I braked at a green light for no apparent reason. I was surprised that I did that.”

“I went to the movies and forgot to pick up one of my friends on the way, and I forgot how to get to her house for around 10 minutes.”

“I went to pick up flowers for a project … ”

And these are all different women.

“… went slightly blank on the way. Had to rethink the directions to the store and where to park.”

“I tried to call a friend and could not remember her phone number. I call this number often. I get very frustrated when I cannot function as usual.”

And then:

“I forgot how to spell ‘Wednesday,’ and I learned that in the first grade.”

Some of these experiences might seem familiar to some of you. Who has had similar experiences? Yeah. (Laughter) Very familiar. That’s what we’re looking at when we’re talking about chemobrain, these kinds of difficulties.

What I’m going to do today: I want to give you a general background, talk about some factors that affect cognitive function in cancer patients, and then I want to go onto the research, because you’re a smart group and I know that you’re aware of the research being done. I want to talk to you about some of the challenging issues that we face as researchers. I’m going to show you a few compelling results.

I’m going to end up that section by asking you: Is “chemobrain” the wrong name? Should we be thinking
about it in a different way? I have a reason for doing that. Then I’m going to ask what we should be measuring, because there’s a controversy in the literature about what actually constitutes chemobrain or cognitive dysfunction among cancer patients, and it matters how we measure this.

Then I’m going to go on to Brain 101. I’m going to talk, in a very non-scientific way, about how the brain works and what your brain is capable of doing. That’s sort of the lead-in to what you can do for cognitive health, because if you understand how your brain works, then it’s easier to implement these sorts of lifestyle changes that can help you with cognition.

What are the factors that are affecting cognition? Whenever you have a complex human process like cognition, there are multiple variables that play into it. It’s not just one thing that causes cognitive dysfunction. Aging, distress, fatigue, illness, cancer itself and other illness and medication all play a role in loss of cognitive function. I’m going to discuss each of these one by one.

Let’s start with aging. We know that there are normal age-related declines in memory and processing speed. Now, this is a young group—you’re young survivors—so you’re not expecting to have age-related changes. But the truth of the matter is that cognitive slowing and these changes start as early as your 40s, and some researchers even think they start in your 30s.

So, what’s normal? In your 40s you’re going to have some volume loss, and you’re going to have some shrinkage of the neurons. That starts as early as your 40s. It accelerates in your 50s and of course beyond that. What we see is really cognitive slowing. It’s not a loss of ability. You are still you. Your intelligence has not changed. Your depth of knowledge has not changed. But you’re going to have more trouble retrieving that information. It’s going to be a little slower, and you’re going to have more trouble putting down some new memories. Again, it’s slower.

Multitasking will become more difficult. By the way, multitasking is difficult. You lose efficiency by multitasking. Even in people who have no cognitive impairment at all, the research tests show that when you try to do more than one thing at once, both tasks suffer. It divides your attention. You may think you’re saving time, but you’re hurting both things that you’re doing.

There’s less attention and retention of detail. You need to pay attention to things to learn them or remember them. What happens is we tend to go for a sort of efficiency where we don’t pay attention to the details. If you haven’t paid attention and encoded them, you’re not going to remember them. You need that time to do that.

In breast cancer, typically, only about 12 percent of women are under 44 years of age when they’re diagnosed. I want you to think about breast cancer as a form of accelerated aging. Any cancer is a form of accelerated aging. It plays havoc with your hormones. It releases other chemicals in your body. So it’s not unusual for someone who’s in their 40s who’s had breast cancer to be having kind of cognitive changes that are more like the next decade, being in your 50s.

Why is it especially difficult for young women? Well, because young women aren’t expecting to have this problem. They’re busy with work, building careers. They’re at a time in their life when it’s really inconvenient to have cognitive loss. If you’re aging, it makes sense and people expect it. It’s harder when you’re younger.

I want to talk now about distress. We know that distress, and in particular depression, has very adverse effects on cognitive function. Depressed and anxious individuals are about 40 percent more likely to develop mild cognitive impairment, which is a mild form of impairment, just like the name says. It’s not dementia. It can be a precursor to dementia in some people, but not all the time. And it just means that these minor changes are a little bit more than what we expect to see for population norms, for other people your age and education.
There are detrimental effects of transient and chronic stress on attention, memory, spatial processing, spatial learning and processing speed. Brief stress impairs briefly. If you have a life crisis, it’s going to affect your cognition for that time. Chronic stress, on the other hand, can impair you permanently. It actually reduces the volume in key areas of your brain that are necessary for learning and memory, like the hippocampus and the frontal lobe. So if you have chronic stress, you need to get it under control.

... We’re going to talk a little bit later about the fact that your brain’s very plastic. It can grow throughout your life, and if you do things to challenge it, you can regain that.

I’m talking about distress. Clearly a diagnosis of cancer initiates a course of stressful events that may continue over an entire lifetime. Was anyone here distressed when they were diagnosed? How about when you heard about your treatment plan, and when you finished treatment? Yeah, like, “Who’s going to monitor me now? What’s going to happen?”

You all undergo a great deal of stress. I want you to consider the possibility that, number one, we said cancer is an accelerated form of aging, and, number two, that some of the cognitive problems you refer to as “chemobrain” are actually related to the life stresses you have as cancer patients.

There’s a recent meta-analysis that shows that young women with breast cancer are more likely to be depressed than older patients and survivors. This was just published in the last couple of months, and it came out of Patty Ganz’s group at UCLA. This was not a surprise to researchers. We’ve seen time and time again that quality of life was worse and distress was much higher among younger patients, because they’re not expecting to be ill at this stage in their life. It’s sort of more acceptable as you get older that things are going to happen and you’re going to become ill. When you’re young, you’re looking for a mate, you’re planning a family, you’re raising children, you’re expecting to be healthy. Cancer is not what you think is going to happen, so of course you’re going to be much more distressed. You have things to do.

You don’t have time for this. You’re worried about what’s going to happen to your family.

I want to talk now about some more data that came out of the Fox Chase study, looking at distress and objective cognitive function. What we did is we gave them cognitive testing. We used an electronic battery. We looked at their processing speed, which is how you process information, how you maintained it in mind, in working memory, and also your language processing, your ability to understand and regurgitate, sort of, language.

For distressed people — and keep in mind this is a very small study; we only have a few people there — for distressed subjects, they’re about half a standard deviation lower. They performed more poorly on processing speed. They were slower. These are standard scores, so the mean, the average score, is 100. What’s considered a meaningful deviation, the standard deviation, is about 15 points. So you can see here that they’re about half a standard deviation lower than the people who are not distressed. What we see is that patients report trouble taking down phone numbers, difficulties doing mental arithmetic, keeping numbers straight in their brain. They feel that their thinking is slow, and this perception is probably very accurate. Their thinking is slow. Now, it’s not very far below population norms that are adjusted for their age. It’s not that it’s serious impairment, but it makes a difference to the person. They’re aware of this slowing. It’s kind of like running a very sophisticated program on an old computer with an old operating system and a poor processor. It’s very frustrating. All the information is there, and it’s eventually going to come up on the screen, but it’s taking too long and you’re a little impatient and you’re worried about it.

I want to move on to fatigue. We promised we would talk a bit about fatigue in this presentation. It’s one of the most frequent complaints among all cancer patients. It’s associated with anemia, and we know that anemia is a risk factor for later dementia and for cognitive problems in older adults. We haven’t studied it as much in younger adults. Anemia causes cognitive decline, cognitive impairment. There are some demonstrated associations.
between declines in hemoglobin and cognitive function in breast cancer patients before they started treatment. This was Lynne Wagner’s work at Northwestern University. So, a lot of cancer patients have anemia. If you’ve had anemia, that’s affecting your cognitive function as well.

The other thing is that fatigue also results from sleep disruption. A lot of you probably had difficulty sleeping when you got your diagnosis, during treatment. It’s a very common problem. If you’re not sleeping, it’s going to affect your cognitive function. It’s going to impair your memory, and it impairs memory consolidation. While you sleep, all that information that you took in during the day is consolidated. It gets stored in your memory in a more permanent way. They’ve done studies with rats where they give them an MRI when they’re learning a maze, and then they give them an MRI at night when they’re asleep. And they rerun that maze in their brains in their sleep. You need to sleep to have good cognitive function.

We looked at fatigue and objective cognitive function, again at Fox Chase. We used the Fatigue Symptom Inventory and the accepted cut point for what is significant fatigue. We looked at response speed on how fast people can organize information, direct their attention to a stimulus—so, if you hear a noise over here, you have to orient to it—and their ability to block out distractions. That’s what response speed is. You can see here that the women who were fatigued scored a full standard deviation lower than those who were not fatigued. That’s a pretty significant difference. Now, it’s not statistically significant because our numbers are so small. However, clinically speaking, one standard deviation below matters. For those women who are experiencing slower processing speeds and response speed, it’s salient to that.

Again, this is only slightly below population norms. I don’t want people to think that cognitive impairment in cancer means you’re nearing dementia, that you have to worry about not being able to function normally. You can. The reason I stress this: I heard yesterday, having lunch with some people, that they heard about a woman who didn’t want to have chemotherapy because she didn’t want to lose her hair. She was going to skip the chemo. I’ve heard people talk about whether they should have chemotherapy because they’re worried about cognitive function. You don’t need to worry about that. You need to have chemotherapy and treat your cancer. The cancer matters. These impairments are relatively minor. I know they matter a lot to you, but in the larger picture, they are not a reason to worry about chemotherapy. The cancer itself alters neurochemicals and hormones in your body, and these have an effect on cognitive function. We know that there are strong associations between cancer and inflammation. The same inflammatory cytokines that are associated with cancer are associated with declines in cognitive function. They’re also associated with anemia. You can see how it’s complicated here. All these things sort of come together to work against you.

Comorbid illness: Now, this is a young group, so you’re likely to have less comorbid illness. Cancer usually affects older patients who have a lot of other physical difficulties. These can also cause cognitive decline. If you have hypertension, heart disease, multiple sclerosis or diabetes, these have a negative impact on cognition. You need to monitor the rest of your health. It’s not OK to say, “OK, I have cancer, and that’s the only thing I’m going to take care of.” You need to look at everything.

Medication: When I talk about medication, I’m talking about chemo. These are just a few of the agents that we know may have cognitive effects, and some of you may have had some of these. Treatment can have these direct or these indirect effects. By direct, I mean that the drug itself passes through the blood-brain barrier and alters your brain in some way, either the neurochemicals or the structure. By indirect, I mean that it sets off a cascade of events in your body that changes hormones and chemicals, and that in turn changes how your brain is working, or also that it’s secondary through symptoms of fatigue and distress caused by your treatment. There are some treatments that actually can cause depression. I don’t think they’re widely used in breast cancer patients, but interleukins and things like that are known to have severe depressive effects.
Endocrine therapy: Aromatase inhibitors have been, and selective estrogen reuptake, have been studied. I’m going to get to that in a minute and talk about some of those studies. We know that estrogen is necessary for cognition. We’re a little bit confused about it since the Women’s Health Study came out, because it turned everything we expected upside down on its head. Estrogen replacement didn’t work, but that was largely because of the particular drug that was used. If you’re inhibiting estrogen, there’s some concern that it’s going to affect your cognitive function.

Evidence from animal studies shows that for platinum-based drugs, it actually does permeate and modulate the blood-brain barrier. It causes neuronal degeneration, and it causes myelin thinning. That’s the white matter in your brain that helps you conduct impulses and helps your brain communicate. An animal study with 5-FU, [fluorouracil] and methotrexate showed that it impaired spatial learning and memory. Remember, this is in rodents, not people. There is a difference. It impaired working memory and tasks that were associated with the hippocampus and frontal lobes in the rodent. We extrapolate that to humans, but sometimes, when you actually do the human studies, you get a different result. We just don’t know yet. They haven’t studied these specific drugs in humans. Those trials are being done now, and we’ll know more later.

Another problem is study participants. We have a tendency to clump together patients with different stages of disease and who had different treatments. The reason that’s being done is because it’s really hard to get participants in this research. I can tell you: I’ve tried. When someone has just been diagnosed with cancer, and they have all of these tests they have to take and they’re running back and forth and they’re trying to make arrangements, trying to schedule them to come in for an hour, hour and a half to do testing is very, very difficult. They need to have larger samples, so they clump in people who are in different places. The problem with that is if you have early-stage disease, your treatment is going to be very different than someone who has late-stage disease, and we really shouldn’t be comparing it.

One of the problems is that different researchers are using different tests of cognitive function. People use what they’re used to using, what they know how to use. They’re using the computerized program that they bought, and they don’t want to change that. If you have different measures being used in different studies, it’s very hard to compare the result. Some measures are more sensitive than other measures, and there are different standards for cognitive impairment. In some studies they’ll say one standard deviation below age-adjusted and education-adjusted norms is a problem, is impairment. In others, they’ll say one and a half. In others they’ll say two. Then they start naming, well, it has to be in two domains of cognitive function. So, it’s kind of all over the place and not standardized enough for us to compare studies. That’s a problem.

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I want to talk now a little bit about the research. I’ve been doing this for 10 years, and there are difficulties. We’re getting better at it. We’re learning. There is now an international task force on cognition and cancer [International Cognition and Cancer Taskforce]. They’re meeting next month in Paris. I can’t go to Paris. I’m so disappointed. (Laughter) They’re trying to fix the research and set some standards so that we’re doing uniform research that really gives us answers that we need.

Another problem is the comparison groups. There’s some controversy over this. What’s an appropriate control group for a group of women who have breast cancer, having chemotherapy? Is it healthy controls? Well, what is healthy? When you pick a group of women from the area and base it on them not having cancer, does that mean they don’t have other illnesses that can affect cognitive function? It does not, and people are not adequately screening to see what other health issues they have. They’re also not screening to see if they have a history of psychiatric disorder. If you’ve had a long-term history of depression, you’re likely to have cognitive impairment. Depression kills neurons. So, if you’re not screening for that, it’s really hard to make comparisons.
The other control group is local treatment. If you’re having local treatment, most likely you have a lower stage of disease, so it’s also not a good control. We’re trying to figure out how to do that.

What do we mean when we say we’re measuring cognitive function? We measure it in two ways. I’m going to talk about objective cognitive function, and that’s using standardized measures. That’s real neuropsych testing. Then we’re going to talk about perceived cognitive function, PCF—the patient’s perspective on what’s happening.

In objective cognitive function, we’re looking at these standardized tests and we’re looking at different domains of function. We’ll look at language fluency, how fast you can generate words using particular letters, or maybe category fluency, if I say I want you to name as many animals as you can think of. Your general memory, executive function—that’s how you organize information, goal-directed activity. It’s what we generally think of as higher human cognitive function. That’s like the big seat of cognitive function. Visual/spatial processing, if you can find your way through the maze of a building or this hotel. (Laughter) When I did my postdoc at Penn, they had these sorts of underground tunnels that lead between buildings. No one could understand why I was constantly getting lost—like, they thought that I should figure it out by now. I just couldn’t do it.

Perceived cognitive function: It’s your experience of cognitive loss. What patients report to us is that they have terrible word-finding difficulties. People have spoken about being in a meeting with their boss and not being able to find the words to explain what they’re working on. For me, I used to go to meetings when I first came to Fox Chase. I was serving on a committee, and I had to review protocols and present to the group. I was so terrified that in front of this room full of doctors and scientists, I would screw up and not be able to find a word and I would look stupid in my new job. So, I would write it out—every single word that I wanted to say—and read it. It’s an issue.

How do we measure it? Here’s a checklist. We give you a number of items and we ask you, “Did this happen to you? How frequently did it happen to you?” It’s kind of a checklist. Or we might interview people. …

… We call this a patient-reported outcome, or PRO. And we use PROs for many cancer-related symptoms. We use them for fatigue, we use them for depression, we use them for pain. There is no standard test for pain. No one hooks you up to a machine to measure how much pain you’re having. No one says to you, “You’re not really having pain because it didn’t show up on this measure.” No one does that for fatigue. We give you a patient-reported outcome. We give you a checklist or we ask you about it, and we accept that as fatigue. We accept that for your level of pain, and we accept that for depression. OK?

We don’t do that for cognitive function. There’s this battle between researchers, where some say if it doesn’t show up as a significant difference on cognitive tests, on objective cognitive function, then it doesn’t exist. Well, what’s the problem with that? It minimizes your experience. What’s happening is very real for you. Whether or not it is below population norms is not relevant. What matters is if it’s a loss for you, if you’re not performing as well as you performed before. For most of us, cognition is who we are, how we think, how we reason, how we present ourselves, how we speak. It’s how we see ourselves. And if that image, that self-image changes and we’re not functioning as normal, it is a serious loss.

There are some challenging research issues. There’s no congruity between measures of objective cognitive function and measures of perceived cognitive function. Article after article, you will see perceived cognitive function did not correlate with objective measures. What did it correlate with? Depression and fatigue, over and over again. That is a consistent finding. It’s a measurement issue. It could be that some of the objective tests we use are simply not sensitive to the kinds of mild impairment that cancer patients are having. They’re designed for more traumatic types of dementia or brain injury.
But recent evidence has been accumulating that shows that patients’ cognitive complaints—and this is not just from cancer; this is in aging adults as well—map on to real changes in brain structure and function. Even if objective tests are normal, there can be differences that are viewable on imaging studies of the brain, and they correlate with patients’ reports of difficulties with cognitive function.

This is a very interesting study. It was done by Bob Ferguson, who’s in Maine now, Tim Ahles and Andy Saykin [and Brenna McDonald]. full ... What they did is they took twin sisters, identical twins. ... One had breast cancer and one did not. They gave them tests of objective cognitive function, and they gave them tests of perceived cognitive function. There were no differences in objective cognitive function. There were profound differences in perceived cognitive function. The sister with cancer had a lot of cognitive complaints. Things were not going well for her. They put them through an MRI, and, in fact, there were structural changes in the sister who had cancer.

We know that measurable neural deficits—and this was just, you know, it’s one set of sisters. They haven’t published the full article yet; there will be more pairs of twins. But there are changes in the brain that we’re not picking up in our objective cognitive measurements.

This was another study. They looked at patients who were having chemo, those who were chemo naive and a group of healthy controls, whatever healthy means. They found that there were differences, that there was impairment in the tracts in the brain that are associated with memory and learning. It’s another study that shows that there were, in fact, changes associated with women who had chemotherapy.

WOMAN: Can you define what you mean by chemo naive?

PAMELA JOYCE SHAPIRO, PhD: They have not had chemo ever. Yes.

WOMAN: That’s interesting. I had an MRI a couple of weeks ago, and they found specks from here all the way down to the back of my brain.

PAMELA JOYCE SHAPIRO, PhD: Mm-hmm.

WOMAN: They said that it could be complications from chemo ... but how do I really know that’s what it is? They haven’t really gone into detail to say that “you have chemobrain.” I’ve never told them that I have...

PAMELA JOYCE SHAPIRO, PhD: I don’t know, and that’s a very interesting question. There are no diagnostic criteria for chemobrain. It’s not an entity that really exists in the books for people to go, like, you have to have this, this, this and this, and your scans have to look this way. So, I can’t actually answer that.

I can tell you that several months into my chemotherapy, they did brain scans on me because my cancer was in my face. My primary physician called up and he said, “I have some concern. It says you have greater than normal volume loss for a woman of your age.” So, I think for a lot of people, if you have an MRI, you may find that there is some volume loss that is a little bit accelerated. But that’s consistent with cancer being an accelerated form of aging, whether it’s through the treatment or the cancer itself. Then there’s this lack of systematic patterning in the studies, in cognitive function. Some people have chemobrain before they start chemo, before they start treatment. Some people have chemobrain during chemo. Some people get it after they’ve finished treatment.

Yes.

WOMAN: In any of your studies ... some of us are young mothers—[we have] “mommy brain.” It feels like it’s compounded. Before I had cancer and before I had chemo, I definitely felt like I had that mommy brain, and then now on top of that, this feeling of—on top of that, I feel like I’m a non functioning person.

PAMELA JOYCE SHAPIRO, PhD: That’s a very interesting point, because we have a lot of terms for difficulties
with cognitive function. There’s pregnancy brain. There’s menopause brain. There’s mommy brain. You use your brain, and you have to use cognition every single day—it’s what we as humans are—so a lot of things are going to affect it. If you have more than one thing affecting it, it’s going to be compounded.

Mommy brain tends to be an issue with distraction and attention and having too much to do all at once, not with having any kind of insult to your brain.

We have, you know, different patterning, and it’s hard to say what’s happening and when it’s happening, because they’re kind of all over the place. Pretreatment cognitive function is especially interesting because you can’t call something chemobrain if it happens before anyone has had chemotherapy. Right?

What do we know about pretreatment cognitive function? Prior to surgery, breast cancer patients have more problems with attention than healthy control. That’s a given. About 17 to 35 percent of breast cancer patients have measurable cognitive, objective cognitive deficits before they start chemotherapy. Low hemoglobin, as I mentioned before, is a predictor of pretreatment cognitive function, and you can have anemia not just from chemotherapy but from having cancer. Self reports of poor cognitive function, as I said before, associated with psychological stress and fatigue. Many cancer patients are fatigued before they start treatment. It’s not just the result of chemotherapy. The whole process is extremely fatiguing.

I want to look a little bit at patterns of objective cognitive function. In the PREPARE trial, and this was done in Germany by Kerstin Hermelink—she found that about 30 percent of breast cancer patients were impaired at baseline, before they had chemotherapy, 27 percent declined after they completed treatment, and about 28 percent improved after treatment. So, you can see, it’s kind of hard to decide what’s happening.

This is a study we did at Penn. It’s just coincidental that the ends are the same. This is not objective cognitive function. This is perceived cognitive function. We gave them a checklist, because it was a secondary kind of analysis. You can see that 44 percent were impaired at baseline, before they started. If that mean is 100, you can see that they’re below where they should be. During treatment, they rebounded—they were back up to normal. You have to think that might be stress-related, because in treatment you’re going, “OK, I know what I’m doing now and I’m getting treatment and we’re going to fight the disease and we’re going to win.” Post-treatment, they declined again a little bit—but that’s 44 percent.

Thirty-two percent had this continuing decline. They start off fine, they go down a little, and then they go down a little bit more after treatment is completed. … This was 12 months after treatment—we don’t know what would happen if we continued to follow them.

Then 24 percent had what we consider chemobrain. They start out high, they drop during treatment, and then they come back to normal.

What was associated with having lower pretreatment cognitive function? If you were college educated. Why? Because most likely you’re in a job or position that requires you to depend on brain power rather than physical energy, so you’re more aware in your everyday tasks that you’re slower. Greater distress, as we spoke about, and greater fatigue—there they are again.

This is a more recent trial. I wanted to draw attention to the numbers. This is one of our bigger trials. He started off with 42. By the time he did the second assessment, he was down to 37. At the end point, we’re down to 28 people. We can’t do research with 28 people. We need national clinical trials where everyone is cooperating together and we get thousands of people to do the research so that we can really make conclusions. We learned this from the Women’s Health Study. When you look at small, individual studies, you get one outcome. When you look at a large study over time, the outcome can be completely different.

So, 21 percent were impaired at baseline, 65 impaired during or shortly after treatment, and 61 impaired five to
11 months after. These were sort of the strongest results we’ve seen so far, with the most impairment. Twelve of these 17 showed continued decline, that graph where it went down like this, but five of them presented with late-onset decline. They were OK earlier on, but it was after they finished treatment that they started to have this decline. That’s an interesting finding. We don’t have enough long-term data to know what happens five years out, if there’s going to be continuing decline.

Endocrine therapy and cognitive function: This was the Breast International Group. They did a randomized trial, five years of adjuvant therapy with letrozole, tamoxifen or sequential therapy. After five years of treatment and one year after treatment completion, they looked at cognitive function. This was a secondary study as part of this trial. They found moderate improvements in cognitive function after treatment stopped, for all study arms. It didn’t matter what the drug was. And women on tamoxifen had poorer global cognitive function at both assessments. Tamoxifen, there are reasons—I won’t go into it now, but there are chemical reasons why it could have negative effects on cognition.

This was another study where they actually asked people about difficulties at work. And people who had past recurrent tamoxifen or aromatase inhibitors were compared to people who had no history of endocrine therapy at all. They found it was not related to objective cognitive function, objective, and it was only moderately related to perceived problems at work with attention and work completion—so, again, mixed results.

This is Kelly[Anne] Phillips. They did a systematic review of seven studies that looked at endocrine therapy, and this was the conclusion:

“The available data do not support the hypothesis that aromatase inhibitors adversely affect cognitive function or that aromatase inhibitors might have a more adverse effect on cognitive function in comparison with tamoxifen.”

Again, you have this thing where you see individual studies find something, and when you combine them together, the result is different. The truth is we’re not where we should be. We just don’t know.

Is chemobrain a misnomer? This is the answer. (Laughter) All of the above. Sometimes it’s chemotherapy. Sometimes it’s not.

Are we measuring the wrong thing? Well, we’re not there yet in terms of measurement, but I think it is really important that we remember that what is important is what the cancer patient is experiencing and how it affects her everyday life, and not what the score is on an objective test of cognitive function. OK? If I give you a verbal fluency test and you do well, you have the vocabulary and you spit out lots of words that start with F, it doesn’t mean that, when you’re in a stressful situation, sitting across from a boss or having to address a room full of 100 women, you’re going to find the word you need and not stumble over it.

The implication for patients is that if we emphasize objective cognitive impairment, we risk dismissing valid concerns of the patients who are struggling with these issues. It’s also, more importantly, a missed opportunity for intervention. There’s no reason to say to someone, “You did fine on this test. We don’t need to give you any help. We don’t need to work with you.” You should be able to get cognitive help to do something, to have an intervention, to relieve distress, to work on those issues that are a difficulty for you.

The take-home message—I love this poster: “If you don’t remember, forget about it.” (Laughter) A retired professor at NYU did that with his wife, but maybe you can’t. Whether it’s clinically relevant, these deficits are personally meaningful, and they deserve our attention.

I want to move on to Brain 101. Before we talk about what you can do, let’s talk a little bit about what your brain can do. Your brain can grow new neurons for your entire life. It can make new connections. It can learn. Recent advances in neuroscience have shown the remarkable
plasticity of the human brain. In response to new learning, your brain will actually grow.

I want you to think about your brain—this is the unscientific part of the talk—as an orchestra performing a symphony. I want you to think of the conductor as executive function—that’s your frontal lobes—the musicians as your knowledge and your memory, the instruments as your cells and neural pathways, and the sheet music as sensory input. Orchestras play beautiful music. We expect that. But the individual components of the orchestra do not make this music alone. They have to all work together to put out that symphony. Right? You need every single piece of that. Your brain is the same way, so you have to maintain the health of all the parts of your brain.

I want you to think of the conductor as your brain’s prefrontal cortex. That’s executive function—thought-planning, goal-directed behaviors. He observes, directs and coordinates. If you think about a conductor, he’s always on stage and performing. He knows every piece of that music, and he directs everyone in the orchestra, every musician. Very critical. Different parts of the orchestra may stop and have a rest—they’re not all playing at the same time—but executive function, your conductor, is on all the time. That’s why we see executive function deficits in patients with breast cancer, because everything comes together, and the part that is always on is overstressed and overtaxed.

This is structure and process. If you think of the instrument as your cells, an instrument needs to be tuned. Your brain needs nutritional support. You can’t neglect that. It has to be fine-tuned and ready to perform.

The musician, your neural processes, needs to know how to play the instrument, how to read the music, when to play and when to rest. How does a musician know that? Is a great musician a person who can play only one thing? No. He probably knows lots and lots of music, and he probably plays many different instruments. This is true of your brain. You need to make your brain a better musician by learning new things and practicing and making them become easier for you. You can’t expect to learn the way you did when you were young. It needs more work, it needs practice, and you need to challenge it with new activities.

Let’s talk now about what you can do. You need to exercise your brain. It’s a use-it-or-lose-it phenomenon. Your brain is an intellectual. It likes to be challenged. It likes to learn. That’s what it’s meant to do. You want to try to solve problems. You want to expand your activities and give it new things to learn. Learn complex tasks. You can’t just repeat the things you normally do. It has to be something new. It’s like working out. If you do the same exercises every day, that’s great. You’ll stay fit, but you won’t grow new muscle. You have to keep increasing the weight.

Exercise your body. Study after study has shown that the single best thing you can do for your brain, in fact for your health, is to exercise. It reduces fatigue. It increases the oxygen to your brain. It increases chemicals that support cognitive health, so your brain-derived neurotrophic factor has been shown to be increased. The neurotrophic factor that helps you learn and remember things increases with exercise. After a three-week intervention, it increased. It improves your mood, and we know that depression has an effect on cognition. Overall, long term, it reduces your risk of dementia.

Exercise is the most important thing you can do. Walking is fine, 30 minutes a day, three times a week. More is better. Walkers are 25 to 30 percent less likely to develop a form of vascular dementia. It’s very important for cognitive function. There was a professor at MIT, a neuroscientist, who had—and this was before—has anyone heard of TrekDesk? Well, there’s a treadmill that’s made now that has a desk on it, so you can work going one to two miles an hour. He had one rigged up in his office years ago so that he could work while walking, because his research showed him that this was that important.
Socialize: Your brain likes company. Social support is consistently associated with better cognitive function in the elderly. We haven’t really looked at it in younger people, but we can extend it and expect that the same thing is true in young adults. Social support protects against cognitive impairment following stroke, and it reduced the risk of dementia. Turns out it doesn’t matter if the social support is good or bad. If you fight with your siblings, if you have a negative relationship with someone at work, that exchange, that being around people, whether it’s good or bad, it all helps with cognitive function.

**WOMAN:** Is it a paradox?

**PAMELA JOYCE SHAPIRO, PhD:** It’s not a paradox. Humans need social company and social exchange. Even if it’s not the best—I mean, hopefully you have a great relationship, and that’s better, but even if it’s not the best, it’s better than nothing. It’s better than being isolated. Rats that are isolated in the cage don’t do well cognitively.

Eat healthy. I am not a nutritionist, so I never dwell on this, but your neurotransmitters need nutritional support: B6 is essential for memory; choline is essential for learning and making your brain cells grow; omega-3 fatty acids, antioxidants and calcium. Calcium is not just for your bones. It helps conduct the impulses in your brain.

Meditate. It has been shown to increase cortical thickness in MRI scans. People who meditate have thicker prefrontal cortexes. It improves your sleep, and it improves immune function—all very good things for cancer patients.

Then, if it’s really bad, you can medicate. Modafinil improves memory. In fact, it’s very popular among college students on campuses, illegally. If you have depression, get treatment, although I don’t know if you’ve seen the recent studies. It’s very important that—only if you have severe depression—you take antidepressants, because they help if you’re really clinically depressed. If you have a mild depression, they do nothing. Placebo works just as well, so why take the chemicals?

Get informed. This is a very good resource, [the blog] YouBrain After Chemo. She called me up when she heard I was doing a talk last year and said, “Will you tell them about my book?” I said, “Not without reading it.” So she sent me a copy, and it’s a very good resource, so I do recommend it.

If there are any healthcare providers—I think this is pretty much a patient and survivor audience, but you have a right to ask to be screened for fatigue and depression, to ask for psychosocial support, to get education on symptom management so you know what to do, stress-reduction techniques and cognitive skills training. I’m a fan of cognitive skills training. You can find brain games online very inexpensively. The research is just beginning to come out, but they work.

I’m going to open it up to questions now, but I’m going to leave this on the screen while we do that, because I found this and I love this little poem, and I think it characterizes what we all go through.

**LORI ATKINSON:** I just want to remind everybody who has questions, I know it’s kind of tight in here, but we do need the microphone, so you can talk in the microphone. Just feel free to get up, and stand and wait if somebody’s in front of you.

**WOMAN:** OK, getting back to the chronic stress, how could we eliminate that or —

**PAMELA JOYCE SHAPIRO, PhD:** Knowledge is power. You need to know that stress is not good for your brain or for your body. It’s not OK to say, “Oh, my life is so stressful,” and not do anything about it. Meditating is good. Take yoga. Exercise reduces stress. Look at your life and the things that are stressing you out. Some things you can’t change. You can’t change the fact that you have cancer, but how you deal with it can be a choice. You owe it to yourself and to your family to reduce stress as much as possible so you function in the best way and you remain healthier.
Is there a magic pill to reduce stress? There is not. You have to make lifestyle changes.

**WOMAN:** In your practice, in the circles that you’re in, do you encourage patients and women like us, or is there a forum where we can be encouraged to take a class in this or take up mechanics or … learn something new and see where that—can we participate in research studies where it’s like, “Yeah, I decided to learn to play the violin and, dang, my chemobrain’s lifted”?

**PAMELA JOYCE SHAPIRO, PhD:** Yes. I advise people to do this. I’m not a clinician. I’m a researcher, so I don’t get to talk to patients as much as I would like. We were trying to fund an intervention trial where we would give people support and education and cognitive skill training and test them before and after. We didn’t get funded. We came really close, but we didn’t get funded. The bottom line is, you can’t do research without money, so we weren’t able to do this.

I’m working with the [Cancer Support Community](#) now. We’re looking for a way to find some funding, one way or another, so that we can do a trial of this. We would be working with patients and helping them to get sort of training and expand and practice new skills along with the social support of other people who are going through what they’re going through.

If you know that these things help, you can go out and find them on your own. Take a class.

**WOMAN:** What’s the name?

**WOMAN:** Lifehacker.com. It’s a fantastic website. It’s really cool. It’ll be like, you know, how you can gig out your iPod to be something else. It’s really neat. Some of it is extraneous or weird. I don’t remember the title of the article, but it compiled a list in one place of all the free online college courses. … Some of it is in, you know, electromagnetic engineering or something.

**PAMELA JOYCE SHAPIRO, PhD:** Right.

**WOMAN:** But some of it was just, like, how to learn how to reduce your stress, some of the more practical things.

**PAMELA JOYCE SHAPIRO, PhD:** Go ahead.

**WOMAN:** OK. I’m being brave. I’ve been passing out cards for [gutzkygirl.com](#), which is the playful oncology website, and I am in the completion of a book titled *Speak Slow, I’ve Had Chemo*.

With that said, I guess I have to be vulnerable and up here to help others. I had the three years of infusions, and that was the regular breast cancer drugs, the Cytoxan, the Taxol and Herceptin. After the three years, I could not go into the grocery store. I had to put earplugs in my ears, or I’d go in and I’d leave. I was unable to match my socks—I mean, simple things that you do in your house. Before that, I know, I’ve had some attention deficit disorders, but this has put me over the top.

So, to have compiled this information in this cute, playful book, I’m proud of myself. But every day is still a struggle. People look at you and they look at us and they see that we’re young and beautiful, even after all we’ve been through. But internally, that’s what this little book is about. It validates our feelings.

I guess I’m struggling still, to this day, five years later, still grabbing the word, still needing a 10-second pause or arguing on the phone with the insurance company when they rattle off, “Can you please give me your birth date, your address,” duh, duh, duh, duh, duh, duh, duh, duh. It’s like a machine gun going off. Help me. (Laughter)
PAMELA JOYCE SHAPIRO, PhD: OK.

WOMAN: Do you all feel this way? (Applause)

PAMELA JOYCE SHAPIRO, PhD: You do have to slow down and you have to attend to things. Your mental clock is faster internally than the person who’s watching you perform, so it seems like a long time to you. It doesn’t really appear that obvious to someone else. We’re our own worst enemies. We put pressure on ourselves to rattle off the answer quickly because we know we’re having these problems. Don’t. Take the time that you need. You will look thoughtful. (Laughter) You will look intelligent. Make people wait.

WOMAN: I’ve seen some conversations on support groups about ADD medications being used, and I wanted to get your opinion, because I actually was considering it and forgot when I went to my oncologist (laughter) for my six-month checkup. I was going to ask him about that, like, “Hey, want to give me some Adderall?” I’d like your opinion on that.

PAMELA JOYCE SHAPIRO, PhD: We don’t have research on that with patients. We don’t know whether it works or not. I’m not a medical doctor, so talk to your physician, but really look into what the side effects are and what he thinks it might do. Alzheimer’s disease is a very specific pathology of the brain. We know what it does to the brain, and we’re targeting those things that go wrong in the brain. Chemobrain may not be like that in any way, shape or form, so those drugs may not have the effect that you would like them to have. Before you put something in your body, make sure you know what you’re doing.

WOMAN: I take a lot of ADD meds. I take a lot of Adderall. I mean, it helps to mitigate it—like, I’m a mess without it—but it doesn’t solve the problem. It’s not an answer.

PAMELA JOYCE SHAPIRO, PhD: Go ahead.

WOMAN: Do you think there’s any relation to the hormones that chemo—inducing menopause, for example. Could that be compounding? Is that something that, again, tamoxifen might also, because of its relationship to estrogen, is that -

PAMELA JOYCE SHAPIRO, PhD: Yes. That is the thought.

WOMAN: Is there hope? I’m not doing tamoxifen, but I’m hoping that menopause will end and I’ll come back to cycle. Is there hope that when that happens, my brain will come back?

PAMELA JOYCE SHAPIRO, PhD: We know that estrogen is important for cognitive function. The results on tamoxifen and aromatase inhibitors are very mixed, so we don’t know that that causes the problem. In theory it could, and it is possible that you will feel better when you start functioning again normally. Estrogen is important, but we all go through that.

WOMAN: I see a neuroendocrinologist, and he doesn’t have the answer. Has there been any testing theory along with that? My periods came back, and then the chemobrain really set in after that.

One thing that he thought was that with chemo … the suddenness of the menopause as opposed to the transition, that kind of puts the brain into shock, and then it starts overcompensating. It is kind of the estrogen loss that would come with it. But… [inaudible]

PAMELA JOYCE SHAPIRO, PhD: …They have shown that women who have abrupt menopause have much more severe cognitive difficulties than women who have gradual. The research does support that. You know, one month I was fine, and the next month I’m never going to have a period again. It makes a difference.

WOMAN: I just want to say, I’m a patient at Fox Chase, and I love the integrative approach that you are incorporating. I find that very beneficial, because in my journey I waited 11 months to have surgery because I did a lot of
alternative healing. I think it’s crucial, crucial, crucial that everyone all over the planet do integrative health. I think it’s really important, because there are other components that are left out.

I also wanted to say, as a mental health therapist for almost 17 years, I highly, highly, highly recommend counseling to everyone. (Applause)

PAMELA JOYCE SHAPIRO, PhD: Yeah. If you’re distressed or depressed, it will help. The research shows that talk therapy is actually a lot better than antidepressants, except in the most severely depressed.

WOMAN: Yes. I’m actually a family practice physician, and prior to my own diagnosis and chemotherapy, I was under the same assumption, that most of chemobrain was really fatigue, depression, stress. After going through it, and I know—I was under stress after my surgery; I had a month between diagnosis and surgery, another month between surgery and chemo—there was a definite change when I went through chemo in the way my brain functioned, the way it processed things, word recall, all of those things. I am now a firm believer in chemobrain. I do think it’s probably multifactorial. There are a lot of different things that go into it.

I do encourage you guys to talk to your physicians and try to explain to them. They don’t always seem to listen to what you’re saying, but most of them will. Find a new one if they don’t. It has made me a better physician.

I was going to ask you: Is there anywhere we can find information on getting involved in the research?

PAMELA JOYCE SHAPIRO, PhD: Someone just complimented me on the integrative approach at Fox Chase. I have to tell you that I tried for five years to get cognitive testing implemented as a patient service at Fox Chase. It didn’t happen. I tried to get distress screening. They’re just now again talking about it as routine. I am no longer there because my grant did not get funded. That’s why I’m an adjunct, not assistant research professor anymore. We need money to make these things happen.

In terms of getting involved, I would say look at the International Cognition and Cancer Taskforce. If you look that up, you will come to a website, and they will have a list of researchers. You can try to contact them at their institutions and see if there’s some way you can be involved.

WOMAN: Can we have that up on the website after the conference?

PAMELA JOYCE SHAPIRO, PhD: … I didn’t print out the handout because I want to save paper and it was kind of lengthy, but they do have information on resources and websites and programs that I think are beneficial. I can send them to you or make them available online.

WOMAN: I definitely agree with everyone about the chemobrain. I had the same experience, and I had an actual menopause—whatever, the chemo pause—and I think that’s when my chemobrain became worse. That was when I thought I should be better, you know, six months later after treatment.

My question is: What was the UCLA research that you did or that you provided about the young women more likely to be depressed than the older patients? What was the name of that article?

PAMELA JOYCE SHAPIRO, PhD: I don’t remember the first author. I know it was Patty Ganz’s group. But if you Google “young women more likely to be distressed,” or “young women with breast cancer more likely to be distressed meta-analysis,” it will come up. The exact article will come up, and you can access that.

WOMAN: Just to kind of give a little story about what happened with me, you know, I guess all of us are overachievers in the room. I put my grad school on hold while I was taking my chemotherapy and going through treatment. Then last year, when I started back going to school, I actually failed a course. I mean, that’s something that never had happened to me before. You’re talking about the mental stress of, you know, trying to get back in the swing of doing things, and then in graduate school...
and to fail a course and be going through college and all of this all your life. It just came all together, seeing other people here say the same things—because I couldn’t concentrate. I didn’t have the same focus with academics. Do you know how we can do that? Just keep studying or—what do you suggest?

**PAMELA JOYCE SHAPIRO, PhD:** Well, you need to reorganize your life in very significant ways. The way you used to study may not work anymore. We know that spaced retrieval works better. If you were the person who could stay up all night and cram for a test, you can’t do that anymore. You can’t sit in one sitting and remember what you need for the test. You need to start from day one in that course, organizing your notes in the best way for you to understand the material, and practice it every day as you go along, and then review two weeks in advance, because that’s the only way you’re going to be able to really know it and remember it. You need to have time for that to consolidate.

There is a subset of women who do have what we consider true chemobrain, who had that decline during chemotherapy and right after. It’s unclear now whether that subset rebounds later. We don’t have the research to know what happens, if that persists or not, or if it declines more. There is a subset of women who do, in fact, experience cognitive loss during and immediately after chemotherapy.

**WOMAN:** I think I fall into that category.

**LORI ATKINSON:** We have time for one more question.

**WOMAN:** Thank you.

**LORI ATKINSON:** I’m sorry to interrupt you, but I don’t want you to be late for the survivor picture.

**WOMAN:** That’s OK. Mine’s just a quick tip. I’m a long-term survivor, and I’ve been dealing with this for a long time, and I’ve had methotrexate multiple times and CMF, et cetera. I feel the same way everybody’s talked about. It’s actually kept me from going to get a master’s degree.

Quick tip: Get yourself—you can find keychain versions—a little voice recorder. It’s awesome when you need to go to the store and you have to remember milk, bread and—I just forgot what the third one I was going to tell you was. (Laughter) I mean, literally on your keychain. Now, you have to remember that it’s on your keychain in order to remind yourself what you have to remember. I know early on that was helpful, just to have a little voice recorder. I think most phones now have them on them. Use it. One helpful little tip I’ve found. (Applause)

**PAMELA JOYCE SHAPIRO, PhD:** I just want to say: Nobody reminded me they had to go back to the introduction and revisit it.

[END OF TRANSCRIPT]