

2003 Chicago Workshop on Biomarker Collection in Population-Based Household Surveys of Older Adults

Proceedings

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Foreword and Acknowledgements

The following proceedings were prepared from a transcript. Bear in mind the informal nature of the workshop; participants' presentations and comments should not be used without permission.

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The Workshop was organized and coordinated by Dr. Stacy Tessler Lindau, with assistance from Jenna Mahay, Adelle Hinojosa, and many others.

The full text of the proceedings can also be found on the Center on Demography and Economics of Aging web site, <http://www.src.uchicago.edu/coa/>.

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Agenda:

2003 Chicago Workshop on Biomarker Collection in Population-Based Household Surveys of Older Adults – June 23, 2003

8:00 - 8:30 am	<i>Breakfast reception</i>	
8:30 - 8:40 am	Introduction: Challenges of Biomarkers and Biometrics in Domiciliary, Population-Based Health Research Involving Older Adults	
		Stacy Tessler Lindau
8:40 - 10:00 am	Biomarkers of Disease	
	Moderator:	Wendy Levinson
	Discussants:	Chris Clark – Dementia, Alzheimer's Disease Myron Cohen – Infectious Disease David Ehrmann – Endocrinopathies Phil Greenland – Cardiovascular Disease Jeffrey Halter – Diabetes
10:00 - 10:15 am	<i>Break and refreshments</i>	
10:15 - 11:45 pm	Biomarkers and Biometrics of Condition and Function	
	Moderator:	Edward Laumann
	Discussants:	John Cacciopo – Stress, loneliness, hemodynamic function Chris Clark – Cognitive function, mild cognitive impairment David Ehrmann – Endocrine (esp. sex hormone) function Martha McClintock – Smell, pheromones, and taste Thomas McDade – Immune function Todd Semla – Medications
11:45 - 12:00 pm	<i>Buffet lunch served, to be eaten during remaining sessions</i>	
12:00 - 12:30 pm	How Can Biomarkers Be Collected in a Population-Based, Household Survey with Non-Medical Interviewers? The Add Health Experience	
	Speaker:	Richard Udry
12:30 - 1:30 pm	Next Steps: Strategies and Infrastructure for Collecting Biomarkers and Biometrics in Domiciliary, Population-Based Health Research Involving Older Adults	
	Moderator:	Linda Waite
	Discussants:	Myron Cohen Thomas McDade William Parish Parminder Raina Teresa Seeman Richard Udry

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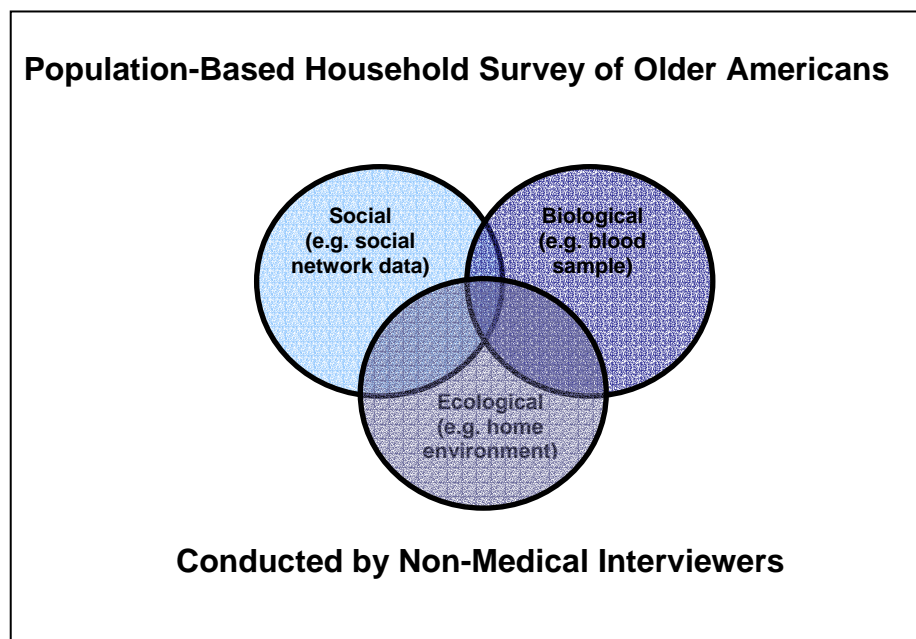
Introduction: Challenges of Biomarkers and Biometrics in Domiciliary, Population-Based Health Research Involving Older Adults

Stacy Tessler Lindau

Integrated Health Model

We propose an integrated health model for population-based household surveys of older adults. The vehicle for collecting information will be non-medically trained, but professional, interviewers. We come together at an intersection where social research about health (including demographic, psychological, sociological, and economic) joins ecological research about health and biomedical research about health, the latter of which has traditionally happened mainly in a clinical domain. We want to think about where these areas of research intersect.

FIGURE 1. INTEGRATED HEALTH MODEL DIAGRAM.



What are Biomarkers?

Many words and phrases have been used to describe the collection of biological specimens in the field. "Biomarker" is not a term commonly used in the clinical setting to describe lab tests like those obtained from drawing blood to monitor health or diagnose disease. However, the assays

performed on specimens obtained in the field and in the clinic may be the same. Other terms, such as biological indicators, biospecimens, and biophysical measurements, have also been used to describe the collection of biological specimens in the field – all of these terms apply. For a more formal definition, we adopt that of Doug Manuel.

Biomarkers are:

“Biological or physical measurements collected from individuals through direct contact or physical interaction with survey participants.”¹

The term “biomarker” comprises a variety of categories of measurement. Biomarkers can measure disease (diabetes, heart disease), condition (strength, endurance, blood pressure, height, weight), function (physical or sensory), and aging (genetic markers of aging), for example. These are the categories of biomarkers that will be the framework for our discussion today. There are certainly many health conditions that can be measured by a variety of kinds of biomarkers, for example cognitive impairment. This condition may be measured by biomarkers of function, condition, and disease.

Interactive Biopsychosocial Model

We propose an interactive biopsychosocial model (see Appendix A), which is a conceptual framework we use in our current project to understand the interrelations of social life, health, and sexuality.² This model builds from George Engel’s “biopsychosocial model.”³ We conceptualize health to include three domains: social, psychocognitive, and biological. (The psychocognitive domain is especially important for older adults, because cognition plays such a critical role in aging.) These domains of health come together to form the health endowment of an individual. Using the model, we can look at the focal individual, but also focus on linking him or her to another individual – a significant other, caregiver, relative, or significant social other. In doing this, we have a way to model health as a multifaceted concept, and as jointly produced between an individual and his or her key social connection(s).

The Challenge

During this workshop, we want to think about collecting biomarkers using non-medically trained interviewers in a population-based household sample of older adults. Such an endeavor would allow us to collect ecological, demographic, psychological, and sociological data, in conjunction with biological data to inform our interactive health model. This would provide us with a more robust picture than I as a physician would get in the course of clinical research, or perhaps that my social science colleagues would achieve in a major nationally-representative survey that did not incorporate biological data.

1 Manuel, D., Flintoft, V. and Glazer, D. (1999). An ICES Report: Physical measures in population-based health surveys: Measures and methods. Toronto: Institute for Clinical Evaluative Sciences.

2 Lindau, S.T., Laumann, E.O., Levinson, W., and Waite, L.J. (2003). Synthesis of scientific disciplines in pursuit of health: The Interactive Biopsychosocial Model. *Perspectives in Biology and Medicine* 46(3):S74-S86.

3 Engel, G.L. (1977). The need for a new medical model: A challenge for biomedicine. *Science* 196:129–136.

Part I: Biomarkers of Disease

Moderator: Wendy Levinson
Discussants: Chris Clark, Myron Cohen,
Philip Greenland, Jeffrey Halter

Levinson: This section will consider the kinds of indicators or markers used now (or evolving) that can help us to assess the health and illness of a population. We hope that each of the discussants can tell us about their experience with particular indicators.

Biomarkers of Diabetes – Jeffrey Halter

Diabetes, itself, is a marker and a predictor of many adverse health outcomes. The spectrum of diabetes ranges from an otherwise healthy, fully-functional person whose blood sugar level is outside of what we consider to be the normal range, to someone who has major problems with their cardiovascular system, kidneys, vision, and sexual function. “Pre-diabetes” has also been coined because there are predictors of who will get diabetes before they are actually diagnosed. Diabetes therefore includes an immensely heterogeneous group of people.

Population data for older adults show that one can identify about half of the older people who have diabetes by simply asking them if they have it. The problem is identifying the other half of people who do not know they have diabetes. A fasting blood sugar test will pick up about half of that half. In order to identify the remaining unknowns, a glucose tolerance test is needed. This requires drinking a standard amount of sugar after an overnight fast and taking a blood sample two hours later. There is no other accepted method for picking up those people.

One can also measure glycosylated hemoglobin, which is an indicator of overall exposure to circulating glucose levels over a several-week to several-month period. This measure can be used clinically to get an overall sense of glucose levels. Glucose levels can be measured at any time of the day with home kits, and we teach patients to take their own blood samples by finger prick. Home glucose measurement gives a general sense on a continuum of a patient’s blood sugar level for clinical purposes.

Pre-diabetes, or metabolic syndrome, is a controversial approach to identifying people at risk. One set of criteria was proposed by the National Cholesterol Education Program, sponsored by the National Heart, Lung, and Blood Institute (NHLBI). There are five things you have to measure, and if you have three of them, you meet criteria for metabolic syndrome: 1) waist circumference; 2) blood pressure, which most people could be trained to do in a home setting; a lipid panel with 3) HDL-cholesterol and 4) triglycerides from fasting (10-12 hours) blood; 5) blood sugar from fasting blood. If a subject met these criteria, then you could test for diabetes with a glucose tolerance test.

- Laumann:** What percentage of the population is diabetic?
- Halter:** Over age sixty, 25 percent have diabetes. 12.5 percent know they have it. The other 12.5 percent do not know that they have it.
- Waite:** So this is a really important measure.
- Halter:** Yes. But, undiagnosed diabetes may not have any effect on one's sexuality or everyday life if they do not have any noticeable symptoms. Furthermore, metabolic syndrome may not have any effect at all on one's social life or sexuality. These situations are not the same as for a person who has diabetes, knows about it, and gets medical care for it. Asymptomatic hyperglycemia is a risk factor that predicts bad things happening in the future, but as far as determining one's current health, it may be inconsequential.
- Waite:** For the purposes of our project, we are interested in predictors of disease. Knowing that people are at risk, one hypothesis would be that a sexual relationship might have implications for the trajectory of the disease.
- Udry:** Of the 50 percent who don't report that they have diabetes, what percentage of those do the doctors know have diabetes? Is it a failure to know? Does that vary with socioeconomic status? Is it the low-income persons who are not seeing doctors who don't know that they have diabetes?
- Halter:** Most likely, there is a match between doctor and patient knowledge. There are people with doctors who do not know they have diabetes, either. In terms of socioeconomic status, I do not know that. I don't think it is a problem particular to low-income. I think there is available data on this from the National Health and Nutrition Examination Survey (NHANES), Part III.
- O'Muircheartaigh:** If one of these people who does not know has gone to a doctor, would the doctor then diagnose this as diabetes?
- Halter:** If they went to a doctor, those previously undiagnosed who have high fasting glucose might well be identified by the doctor because fasting glucose is not too difficult to do. Organizations like the American Diabetes Association recommend screening with a fasting glucose test. Those who meet criteria for diabetes based on a glucose tolerance test will not be picked up by a doctor because there are very few doctors in this country who do a glucose tolerance test to pick up diabetes. They will therefore be left out unless you are doing a research protocol where you really need to know. In Europe and some other countries, they are much more attuned to this. Maybe we should be and maybe we shouldn't, that is somewhat of a debate.
- O'Muircheartaigh:** If they were to do a glucose tolerance test, would they have treatment for these people, or would they just note the case?

Halter: We would certainly pay more attention to the blood pressure. (There are blood pressure criteria specific to people with diabetes because they are at high risk for cardiovascular disease.) We would also look at the cholesterol goals differently and most would recommend a lifestyle intervention, as many of these people are overweight. There are several medications available to lower their blood sugar. Some would argue that these are the patients that we *should* be identifying and treating more closely because by the time they get to the point that it is obvious to everyone that they have diabetes, we might be way down the road in terms of health problems. I worry about that.

Levinson: As part of this workshop, we should also talk about technical issues, such as collecting blood specimens. While I assume that fasting glucose requires a finger-prick, (... hemoglobin A1C), we should also discuss the types of non-invasive techniques that are available. Are there new biotechnological advances that could inform this conversation?

McDade: There are a number of devices that do point-of-service analyses of hemoglobin A1C, cholesterol, and lipid levels, in addition to the filter paper method for collecting, transporting, and analyzing blood spot samples. These options will be addressed further in the last session of the day, which is more focused on the technical issues.

Halter: So you could leave something like that in the household and ask respondents to take their own blood sample the next morning? How well will they adhere to the instructions?

McDade: I have been involved with projects, including a highly-motivated sample of older women in menopause, where respondents have collected their own samples. They pricked their own fingers, put the blood on the filter paper, and mailed it in. So it has been done, but the onus is on the respondent.

Lindau: With regard to blood sugar, I have read about a transilluminating watch that measures blood glucose. Are you familiar with that technology and could you imagine any use for that in terms of monitoring blood sugar level in the field?

Halter: I do not think it would give a sufficiently precise measurement. The technology is advancing, but currently, that type of instrument is mainly used to detect hypoglycemia in patients who are already being treated for diabetes. It is simply a gross measure. My understanding is that if you want to detect the difference between a fasting glucose of 110 and 128, which would indicate whether someone meets the criterion for diabetes or not, it is not going to tell you that.

Biomarkers of Cardiovascular Disease – Philip Greenland

There are six major categories of biomarkers that assist in the evaluation of cardiovascular health: blood, urine, diet measures, activity/health status, cardiac function, and physical measurements.

First, in terms of blood, you have to decide whether your research will require serum and measures that are relatively specific to serum, or if it will simply require cells. We will hear more about filter paper technology later today, but the choice is between a relatively small specimen that can be amplified, or a large specimen that one can bank, aliquot, and store in a freezer for long term. Certainly, researchers today must consider the possibility of looking for markers in the future that we don't know about today. As research moves on, we will start to uncover new biological factors that have an impact on health. It seems that if you are doing a large survey, it makes sense to bank samples for this reason.

Another decision that must be made regarding blood samples is whether the individual respondent should be responsible for taking the sample and sending it in, or whether a technician should collect the blood (for example, if you need a four-tablespoon sample) and keep it on ice. The latter technique has been used primarily in a clinical setting, although the collection is not very sophisticated and could be applied in a home-based setting.

For example, investigators in population studies have sent collection kits to respondents and asked them to take the kits to their doctor to get the blood drawn in a medical setting. Sometimes money is sent with the kit to cover the cost of the specimen collection. The collection can easily be set up so that the serum and the cells are separated, and then the sample can be sent back to the investigators. Procedures like this are common with studies like the Boston nurses' studies that are frequently referenced in articles and newspapers. It might surprise you that those investigators have, by and large, never met the respondents; those surveys have been primarily conducted through the mail.

Finally, researchers must weigh the options of collecting a fasting blood sample or a non-fasting blood sample. There are several assays that require fasting blood, while others can be performed on non-fasting blood. Overall, one gains the most information by collecting a fasting sample and banking a portion of the specimen.

Second, urine samples offer a great deal of interesting information, and they can be collected through relatively non-invasive procedures. Certainly, many of us have purchased life insurance and had people come out to our houses to collect urine (usually after fasting for the morning). Urine collection is extremely easy to do.

The question here is whether your research questions can be addressed using a spot urine. Spot urine measures only recent exposures and excretions. In order to examine more long-term characteristics, such as sodium intake, a 24-hour urine is required. That is extremely difficult to get people to do.

Spot urine is really the most feasible way to collect a urine sample. From spot urine, you can assess many of the excretions in the micro range that researchers find to be predictors of several types of physical conditions.

Understanding what people eat can also be an extremely important indicator of physical and cardiovascular health. The main way that researchers assess diet in population studies is through a Food Frequency Questionnaire (FFQ). The questionnaire asks respondents what foods they have eaten over the last month and how often they have eaten those foods. Interviewers can be trained to assist respondents with the completion of the questionnaire, or interviewers can carry food models to the interview in a suitcase.

While the FFQ may not seem very reliable because it is based on recall of food consumption, it is actually quite reliable and does predict certain things. However, there are other things about FFQs that *are* unreliable, and when people apply them inappropriately they then make inappropriate judgments. For example, if you are interested in caloric intake, FFQs are not useful because they do not provide a reasonable assessment of caloric intake. On the other hand, FFQs are not bad evaluators of macronutrients, and they can provide a window of approximately how much protein, fat, and carbohydrates are in a respondent's diet. FFQs allow researchers to assess whether individuals are receiving adequate protein, for example. In addition, it can help us to understand more about the impact of protein intake on physical function, health, and well-being.

Average time for completion of the FFQ is about 30 minutes. In the Women's Health Initiative, a diet study with women between the ages of 50 and 79, the FFQ has been used quite successfully. Among the geriatric and older adult population, however, there can be additional complications. FFQs have been used with people over 65, but the respondent must have pretty good cognition and remember what he or she ate for several weeks. If the respondent has difficulty remembering, the success of the questionnaire is very dependent upon a good interviewer. In such cases, the administration of the FFQ takes a lot of time and costs a lot of money. While a shortened version of the FFQ or questions targeted at particular intakes could offer some information, it is difficult to know what to look for without using the full FFQ.

Instead of a questionnaire, some biological measures can help us to understand particular intakes. For example, folate and B12 levels can be measured in the blood. These levels, however, are not as valuable as other tissues or as things like fatty acids, which concentrate in the body's fat stores. Unfortunately, it is necessary to biopsy patients to get the most accurate measures of this.

Third, activity and general health status also offer information about cardiovascular health. In population health studies, cardiovascular status can be measured with balance, coordination, strength, and physical activity (for example, with a pedometer that the respondent wears on his belt).

However, these measures are not perfect. For example, a pedometer only measures movement around the trunk. If a person is sitting on a bicycle and not moving his trunk, the pedometer will record no physical activity. But, if the person is walking or climbing stairs, it would record that.

For certain cardiovascular illnesses, like lower extremity disease, which is very common and appears to be asymptomatic among many older people, the crucial question is whether they walk. In our study with older adults, we gave participants a pedometer and instructed them on how to use it. We asked them to wear it for seven days and we called them every day to make sure they were still wearing it. At the end of the seven days, they returned it to us in a mailer. It is feasible to use a pedometer to measure physical activity over a given period of time.

Lower extremity balance is related to vascular dysfunction. Interestingly, we used to teach students that lower extremity vascular obstruction caused particular symptoms, such as pain in the legs and buttocks while walking. But, as we started to study asymptomatic people, we realized that they were asymptomatic not because they did not have vascular disease, but because they had no physical activity.

As a biomarker, balance can be measured by asking people to do chair rises or tandem stands, where you ask people to put their feet one in front of the other. We can quantify this by timing how long a person can stand that way.

Measurements of upper and lower extremity strength are also useful indicators of cardiovascular function, and timed walks (such as a six-minute walk) can be excellent measures of global physical function. The timed walk is low-tech. It takes a lot of time and requires a flat surface or a long hallway. We typically do not do this in the clinic, because it is time consuming. The test is conducted by telling the participant to walk as fast as he can for six minutes. The interviewer walks along with him and keeps track of the time. The test is quantified by measuring the distance walked during the six-minute interval. People with various cardiovascular diseases simply cannot do this. They either walk very slowly or have to stop along the way.

The fifth indicator of cardiovascular health is cardiac function. There is a whole range of things that you can do to measure cardiac function in a home setting. Electrocardiograms, blood pressure, and heart rate can all be measured relatively easily. More high-tech measures, such as ultrasound examinations, could be used if the data are important to a study and an interviewer or technician was trained to perform these procedures.

Not only can blood pressure be measured in the upper extremities, but it can also be measured in the lower extremities (such as the leg or the foot), where the body is more likely develop vascular obstruction. Measuring blood pressure in the leg or foot is a little more complicated than your typical blood pressure measurement, but it requires a relatively similar device.

Measurements of vascular obstruction can communicate a great deal about overall health. We have found that people who have vascular obstruction have health problems, and these problems could explain why they do not walk or shop and often become depressed. We have found that asymptomatic vascular obstruction is related to depression. Vascular obstruction can therefore be used as a surrogate for these things.

Finally, more general measures of physical composition provide information about cardiovascular health. Measurements of height and weight can be taken, and measures of body composition are also instructive. Bioelectrical impedance gives a relatively noninvasive measure of body composition, but it is not as precise as underwater weighing. Underwater weighing provides the best measure of body composition, but it requires an immersion tank and is probably not a possibility for a home-based, national survey.

Lindau: Biomarkers like balance and physical activity could be easily incorporated into the natural choreography of an interview. Many of those things, like standing up, certainly happen in the interview, they just do not get measured. Non-medically trained interviewers need to be trained so that when the respondent stands up at the end of the interview, they are prepared to take key measurements.

Dan Gaylin: We at NORC have collected most of these cardiovascular measures that you mentioned, and after some principal components analysis, we found that there were some very significant indicators. But, we also collected information in a number of areas which were not as useful. Based on the body of literature, do we not have, a priori, some cost-effectiveness measures of what options are most feasible, most likely to be predictive, and most useful across the dimensions in which we are interested?

Greenland: We can certainly boil this down to the most likely candidates – measures most likely to be predictive and indicative of cardiovascular health. The problem is that the most likely candidates may be the most likely candidates because they are already known to be predictive. If you rely on these measures alone, you are only confirming what others already know.

There are some things that seem almost obvious, such as the idea that if researchers can get a blood sample, they should get blood and bank it so that they can go back to it at a later date. But, as soon as you start whittling down the markers that you will collect, you eliminate whole areas that you can no longer examine. For example, if a study decides that it is too hard to look at diet, then the researchers have no option to look at it later or compare it to other measures. These are questions with which every study has to grapple.

Kurina: Part of the benefit of collecting data on some of the predictors that we already know about is that we can then control for these predictors when exploring novel risk factors. For example, by controlling for certain pre-existing conditions, one can get better estimates of the relationship between certain aspects of social life and health.

Greenland: And, controlling for conditions is also useful in learning whether new indicators offer information in addition to measures that we have already found to be predictors.

Levinson: Banked serum is certainly very valuable. For example, crucial early data on HIV was discovered because a study had banked serum collected from gay men in San Francisco, when the researchers were not at all looking for HIV. Years later, the researchers were able to analyze it and examine the prevalence of HIV, after the virus had been discovered.

Biomarkers of Infectious Disease – Myron Cohen

In terms of biomarkers of infectious disease that should be considered, I'm not going to focus on particular areas, but rather I will discuss the larger picture and some general areas for examination.

Each person is living in a microbial world and so a researcher could collect anything from a respondent's house to see what that person is living with in his or her environment. Researchers have collected samples from kitchen counters, toilet seats, and many other places in order to make claims about general health. Also, travel and the presence of pets are important considerations in infectious diseases, and they are items that you need to know if you want to interpret health at a certain age.

In addition to the environment, there are host defenses. Inflammation, for example, is indicative of host defenses going awry and causing some sort of observable reaction in the body. There are a series of host defenses that are useful in preventing infections. These defenses are measurable, depending on what specimens you choose to collect.

Finally, there are two ways to look at infectious diseases. First, the agents of infectious disease are definable. Agents include prions, viruses, bacteria, fungi, protozoa, and worms. Second, by examining a single organ system, we can sample infectious agents living on or in that organ. For example, by studying STDs, you're focusing on the genitals and what infectious agents might be contained there.

In order to assess the presence of infectious agents, specimens can be collected from any site that is accessible, such as the nose, mouth, tongue, vagina, rectum, or urethra. There are self-administered swabs for all of these sites, or specimens could be collected with the help of someone who has minimal training. Using these samples, you can learn about the flora that is in that organ at that point of time. As another alternative, you can "wash" the genital tract by collecting a urine specimen and examine that specimen for particular agents.

Serum or plasma antibodies and history can provide information about microbe exposure over a lifetime.

Levinson: In the older adult population, what do we know about the prevalence of STDs and HIV?

Cohen: We don't know much about HIV, but it is expected to be rare. Gonorrhea and chlamydia are expected to be rare among older adults as well. However, these have not been studied systematically, so our knowledge is from clinic-based studies and reports.

Lindau: But we should not extrapolate from clinic-based information because older adults rarely get tested by their doctors for sexually-transmitted diseases.

- Cohen:** There are not population-based studies of people in that age group for a number of reasons. Some of it is based on belief systems about prevalence. The purpose for finding the prevalence of some diseases is also questionable. Trichomoniasis, for example, is a common disease in older women. Trichomonas is an organism that is generally sexually-transmitted but it can on occasion be found in the environment. The health consequences of trichomonas infection are limited.
- Cultural variations are another complication. Bacterial vaginosis, a change in vaginal flora, results in a watery vaginal discharge. But women living in different countries may have different vaginal flora.
- Lindau:** For sexual function, things like vaginal odor are very pertinent issues and might be a reason to pursue study of some of these conditions. But they vary culturally.
- Levinson:** Is there something asymptomatic or some relationships between conditions and later disease that you feel are important to identify?
- Cohen:** Association and causality among infectious diseases are very difficult to prove, and very frequently confused.
- Raina:** Within the issue of infectious disease in the elderly, is there any discussion of the relationship between environment and viral diseases, particularly which diseases the elderly are more prone to?
- Cohen:** There are a limited number of host defenses (such as skin, mucous, and antibodies), and all of them have been studied in the elderly. Failing host defenses make older adults susceptible to specific diseases, often through reactivation of dormant infections (such as TB and shingles). Measuring host defenses is very complicated in population studies. Skin testing is possible but complex and invasive. Cellular responses can be studied in vitro but 50cc of blood is required to get cells. Antibody studies require much less blood, sometimes just a finger stick or an oral swab.
- Waite:** What about herpes?
- Cohen:** Eight herpes viruses have been discovered to date. HSV-1 and HSV-2 are quite ubiquitous. We can use serum to determine past exposure to any herpes virus. However, most of the herpes viruses would be expected to be extremely common in older adults.

Biomarkers of Dementia and Cognitive Impairment – Chris Clark

I want to begin with a few key concepts regarding the use of biomarkers for the study of dementia and cognitive impairment. First, we must understand that this business is not rocket science, and we have to work the best that we can with data that is available. Second, in considering the usefulness of biomarkers broadly – functional, cognitive, and chemical – the most sensitive measure is really change over time. Focusing on change over time solves many of the potential problems of socioeconomic status, language status, educational status, and cultural difference. Third, in studies of dementia, useful information relative to the entire spectrum from normal to mild cognitive impairment to severe dementia, can best be obtained from an informant, because there is an impairment in insight in all dementing illnesses which reduces the awareness of their cognitive and functional problems. When looking at functional measures of dementia, the best source of reliable information will be a subject’s spouse, adult child, or somebody else who knows them well.

Finally, at least two of three domains (functional impairment, cognitive impairment, and biochemical biomarkers) are needed to adequately assess impairment. Possible biomarkers of dementia include: 1) subjective measures of an individual’s functional change, obtained from a knowledgeable informant questionnaire; 2) objective cognitive assessment obtained from a brief cognitive screen (there is a vast variety of these); and 3) biomarkers linked to pathology, such as F2-isoprotanes.

Annual incidence of dementia in various age groups (Figure 1) is relatively well known, so these data give us a rough idea of expected prevalence.

FIGURE 2. ANNUAL INCIDENCE OF DEMENTIA BY AGE GROUP.

Age	Dementia (95% CI)
60-64	0.11 (0.60-0.16)
65-69	0.33 (0.25-0.43)
70-74	0.84 (0.65-1.06)
75-79	1.82 (1.38-2.38)
80-84	3.36 (2.52-4.47)
85-89	5.33 (3.87-7.30)
90-94	7.29 (4.87-10.8)
95 +	8.68 (4.97-14.0)

Source: Chris Clark.

Functional measures of change include an assessment of performance in daily life activities that relate to memory, language, orientation in time and space, decision-making, and the ability to get from place to place. Impairments that are primarily due to physical or medical limitations are not considered. You need a knowledgeable informant to provide the information and a standardized instrument to collect it. This should reflect how a person functions on a regular basis – not how they did on their best day or their worst day.

With cognitive impairment, the focus is to identify problems in each of the major domains affected in dementia. For Alzheimer’s disease, this primarily means memory, so you want to pick up memory problems that are beyond age, social class, and culture. The most brief, most validated cognitive

screens include those that assess orientation, memory, mental manipulation (a clock-drawing task is most common; see Appendix C), verbal fluency, and delayed recall. In the cognitive screen presented in Appendix C, only impairments are scored, so it is not dependent upon level of education and it works fairly well.

The scores from both the brief cognitive and the brief functional screen define an impairment score.⁴ An impairment score of 0-4 suggests no clinically meaningful impairment, a score of 5-8 indicates mild impairment, and a result of 9 or greater suggests probable dementia.

Within the third area, there is only one known pathological marker of cognitive impairment that is detectable by non-medically trained personnel – F2-isoprostanes. Risk for cognitive impairment can also be identified through genetic information, but that is probably too sophisticated for our purposes here.

F2-isoprostanes are relatively easy and efficient biomarkers to collect for several reasons. They are isomers of prostaglandins, and are stored in cells. They are clinically-stable at room temperature for a day and can easily be measured in cerebrospinal fluid (CSF), blood, or urine. Once they are formed, they don't need further processing and an accurate representation of what is actually in the body can be seen.

In Alzheimer's disease F2-isoprostanes are increased in the brain, and they show low variability. One problem is that in a population-survey, 80 percent of the variation in F2-isoprostanes is related to Alzheimer's disease. But, there is a good correlation between the levels found in urine and blood and the levels found in frontal lobes and the spinal cord. The assay costs about \$50.

Nevertheless, elevated F2-isoprostane levels are not a diagnostically definitive indicator of Alzheimer's disease. They merely extend the information that we can gain from functional assessments. All in all, the gold standard for identifying cognitive impairment is change over time.

Lindau: Could you ask the cognitive screening questions of the individual as well as the knowledgeable informant?

Clark: It might be interesting to compare the answers, but the individual himself will not represent his own cognitive impairment well. He will score just as well as a normal respondent.

O'Muircheartaigh: Are all of the cognitive screeners fairly standard tests? What about for Spanish-speakers?

Clark: None of these tests have been published or assessed with Spanish speakers. Although we have worked with some in our lab, we haven't published anything on it yet. The language barrier is vexing, so there is work that needs to be done, particularly with the use of this battery. There are linguistic issues, in that language is so important in these brief cognitive screens, because each word is very important and a linguistic misunderstanding can skew the test.

O'Muircheartaigh: Would that have an impact on African-American English?

⁴ Please see Appendices for screening tools.

- Clark:** The use of the cognitive screens in the African-American community is very controversial. There are studies that say that you should give African-Americans a couple of extra points and other studies that say that you shouldn't cut them any slack. I think this also depends on the geographic area of the country where you're working. Language is so important when you're testing memory.
- O'Muircheartaigh:** So there is no work being done to construct a battery of this kind that more closely matches community or cultural norms?
- Clark:** Not that I know of; but again, this indicates why longitudinal data is so important.
- Waite:** How do you distinguish between low pragmatic ability and dementia?
- Clark:** The design of the screening questionnaire limits the impact of education. For example, anyone with a 4th grade education should be able to draw a clock.
- Levinson:** What is the mean length of time for completion of this battery among older adults?
- Clark:** For older adults, completion takes about seven minutes. It is well tested and easy to administer. We have taught high school students to administer this battery.
- Mahay:** How long do you allow people to work on a problem, such as the clock drawing, particularly if they are having a lot of difficulty?
- Clark:** We use common sense. For example, people who are demented, as opposed to people who are depressed, will spend a great deal of time working the clock-drawing. Once you've done a lot of these, you can tell whether another 90 seconds will make a difference or if another 10 seconds will make a difference. And, with the clock, in particular, it is quite easy to tell how it will go. As soon as the person has the third or fourth mark in the clock, you can almost predict what that clock is going to look like and you can probably score it right there. So, it really doesn't require a lot of time.
- Levinson:** What is the most sensitive pathological marker for cognitive impairment available today?
- Clark:** The best established and most reliable pathological marker is F2-isoprotanes in the blood. Another approach under evaluation involves the measurement of beta-amyloid 42 in the blood, but it is still very controversial and requires quite sophisticated technology.

Special Presentation on Blood Collection

Methods: Techniques for Collecting Finger Prick Blood Samples on Filter Paper

Thomas McDade

Filter paper cards are used for neonatal screening in every US hospital. The papers are certified to meet performance standards for sample absorption and lot-to-lot consistency set by the National Committee on Clinical Laboratory Standards, and by the Food and Drug Administration regulations for Class II Medical Devices. It takes just a couple of minutes to do a finger prick and collect the blood on the filter paper, and interviewers without medical backgrounds can be easily trained to collect samples. Research participants can also be trained to prick their own fingers and collect their blood on the paper.

Whole blood is dried and preserved on the paper and will remain stable for weeks at room temperature (although the stability of specific analytes in the paper will vary, and needs to be evaluated prior to sample collection). In the lab, small disks of blood are punched out of the paper and then the blood is reconstituted by eluting it in a buffer solution. One can then run assays on the blood samples. Anything that is present in blood can be measured using this method, unless the lysing of red blood cells interferes with the assay. So, ferritin, a measure of iron status, can't be done. Another thing to consider is whether the analyte comes out of the paper easily. Some analytes don't easily come out of the paper.

In theory, just about anything that you can measure in plasma or serum can be measured from the filter paper blood spots, including antibodies. This includes most clinical measures of interest. For example, blood spot assays have been developed for Epstein-Barr virus antibodies, high-sensitivity C-reactive protein, measures of reproductive function, cortisol, retinol, folate, DNA/RNA, and glucose, among others. Other analytes could also be measured, assuming the availability of the necessary reagents, but this requires time in the lab for assay development and validation. Another potential disadvantage of the method is that blood spots on filter paper provide a whole blood measure that may limit comparability with other methods that use plasma or serum. One way to address this issue is to develop a correction factor based on a set of matched plasma and blood spot samples that will allow you to calculate plasma equivalents from blood spot results.

However, a benefit of this method is that you can get lots of samples from lots of people at all ages. Another benefit is that by virtue of drying the blood on the paper, the paper is not considered to be biohazardous unless it is known to contain infectious material. So, labeling and handling requirements for shipping the samples are minimal.

Lindau: How many holes can you punch out of each spot of blood?

McDade: The papers are labeled for five spots of blood. You can get about 7 punches out of each blood spot, so 35 total disks. Assays typically require one or two disks of blood.

Lindau: Can you typically get all five spots from a finger stick? Is that true even for older adults?

McDade: You can easily get two blood spots from a finger stick. Five is possible, but sometimes it takes two finger sticks.

Part II: Biomarkers and Biometrics of Condition and Function

Moderator: Edward Laumann

Discussants: John Cacioppo, Chris Clark, Jeffrey Halter, Martha McClintock, Thomas McDade, Todd Semla

Biomarkers of Stress and Loneliness – John Cacioppo

In America, blood pressure in older adults shows an age-related increase. However, our meta-analysis of the extant literature on social support and physiology revealed that this age-related rise in blood pressure was modulated by social factors such as social support.⁵ Micro-analyses suggested that a tipping point occurs around age 65, where those low in social support show much clearer age-related increases in blood pressure than those high in social support. We recently replicated this result in our population-based study of loneliness and further found that the dimension of collective connectedness appears to be the most powerful social psychological predictor.

It's important in the use of any biomarker, even something as simple as blood pressure, to consider sources of variance in biomarker measurement. These sources include the: 1) person; 2) situation (physiological or environmental); 3) interaction of person and situation (such as reactivity); and 4) instrument measurement error. We need to be particularly sensitive to the interaction term, in that collecting biomarkers themselves can cause stress and reactions that skew the various specimens collected. Even a simple biomarker like blood pressure is subject to “white coat hypertension” effects. Thus, ensuring that respondents are comfortable before taking measurements and obtaining three readings of blood pressure that can be aggregated after eliminating any outlier provides much more reliable and valid assessments of basal cardiovascular functioning. This measurement precision can be especially important to achieve when conducting longitudinal research because individuals are likely to adapt to the measurement procedures across measurement occasions.

The importance one places in the sources of variance in biomarker measurement also depends on comparison groups. If you are comparing two extreme groups – one with high blood pressure and one with low blood pressure – you may be able to suffer more measurement error than if you are looking at subtle differences between individuals in the general population.

Given the importance of making your respondents comfortable before taking basal measures, it might be helpful to say a word about how this might be accomplished. Traditionally, respondents were asked to simply relax once the measurement instruments were introduced, and several minutes were allowed to pass with the assumption that respondents would adapt. Subsequent research

⁵ Uchino, B. N., Cacioppo, J. T., and Kiecolt-Glaser, J. K. (1996). The relationship between social support and physiological processes: A review with emphasis on underlying mechanisms and implications for health. *Psychological Bulletin* 119:488-531.

indicated that not all respondents adapted, and that giving respondents nonevocative materials to read or complete (so-called “vanilla tasks”) actually fostered adaptation across respondents. Thus, establishing a relationship or a rapport with the respondent, perhaps by beginning with a straightforward demographic section of the questionnaire, may decrease reactivity and help you to get better baseline measures of the biomarkers you collect.

Biomarkers of Endocrine Function – Jeffrey Halter

Blood and urine samples are especially beneficial for the examination of endocrine function because they provide integrated information. However, endocrine function and sex hormones fluctuate over the course of the day. Thus, it is difficult to get at what is, for example, the actual testosterone level. There are no algorithms for fluctuation during the course of the day because these things vary for each individual.

Laumann: Does it help to note the time of day when the samples were collected?

Halter: Yes, definitely. But, I'm not sure whether there is a meaningful way to control for variation, as there are many subtleties according to gender, aging, time of day, and other personal characteristics. So, you have to be very careful when comparing samples across these variations.

For the collection of biomarkers in households, researchers need to standardize: 1) when biomarkers are collected; 2) when in the interview sequence biomarkers are collected; 3) the context, including whether the respondent is sitting or standing. Yet, overall changes like aging far overshadow these daily fluctuations.

O'Muircheartaigh: Are there some profile questions that we could add to the questionnaire to get information about where the person is in their day, such as when they last ate and what time they woke up?

McClintock: Documenting where people are in their activity and sleep cycle at the time of collection is very important because circadian rhythms are affected by age and affect most physical functions. How might we go about documenting this or understanding the effect that circadian rhythms have on biomarker collection?

More generally, in evaluating these measures, we might want to think about what the real questions are here. If your questions are about sexual behavior and sexual interactions, you might not want such medically sophisticated measures. You might learn more by assessing bioassays and traits that have a direct effect on sexuality, such as vaginal lubrication, shaving and hygiene habits, and vaginal odor. You might need a smaller group where you validate these bioassays with more molecular measures.

Levinson: What is the relationship between sex hormones and sexual function, particularly in women? Do measured levels relate to libido?

McClintock: It is well-established that sex hormones matter, but it is their receptors that are key— not just blood levels – such as those in the brain or in the genitals. You can have all the hormones circulating in the blood, but without receptor activity, sexual functioning is impossible.

Halter:

Measuring sex hormones can be very complicated. The balance between estrogen and androgen, for example, is extremely important.

McClintock:

But, it's almost as if we know too much about these complex hormones and the way that they are carried in the blood. It is also important to understand how sexual functioning actually happens, on a much simpler level, in addition to the biomarkers.

Biomarkers of Smell, Pheromones, and Taste – Martha McClintock

One of the biggest complaints of people in old age is that they have lost their appetite and enjoyment of food. This has been linked now to the aging and disintegration of olfaction, which diminishes flavors and thereby appetite. Many things that are seen as peripheral, such as olfaction, for example, actually drive aspects central to health, like appetite. If you block olfactory receptors, you cannot taste very much at all, because the tongue has only a few types of taste receptors.

Linda Bartoshuk at Yale University and Susan Shifman at the University of California at San Diego have done massive epidemiological studies of aging related to smell and taste. Measurement instruments have been developed and are very easy to use. For example, PROP receptors on your tongue that taste bitter flavors are very numerous when you are young, but they diminish as you age. By simply applying blue food coloring to an individual's tongue, you can count the white papillae and PROP receptors that are present.

Richard Doty at the University of Pennsylvania has developed an effective smell inventory test, called the University of Pennsylvania Smell Inventory Test (UPSIT). He has run these tests over many individuals to look at the effects of common diseases in older adults. Avery Gilbert is developing a new test called Cranial One. In this test, standard amounts of a compound are contained on a paper. You tear off the cover and a standard amount is released. At a standard distance from the paper, you can measure whether the individual can detect the smell. This is a big improvement on the typical scratch and sniff method. The best method is “snif-n-sticks” which are like magic markers impregnated with controlled concentrations of odorants.

Smell and taste are important beyond the fact that elderly individuals report lower quality of life when they diminish. Based upon the animal model work of Leslie Kay at the University of Chicago and Noam Sobel at Berkeley, olfactory function is a very good signal of what is going on in the cortex. Olfactory deficits, for example, are one of the first signs of Alzheimer's disease and cognitive decline.

Leslie Kay has also documented (with rats) that the behavior of mitral cells in the olfactory bulb is driven more by the meaning of the odor that they detect than by the actual chemical. She has conducted research with rats, in which she trains the rats that an almond smell signals sweet water and a vanilla smell signals bitter water. She delivers the signals and measures the pattern of neural activity. Then, she waits a period of time and retrains the rats in the opposite direction, so that almond signals bitter water and vanilla signals sweet water. By doing this, she has shown that the neurons fire according to the meaning of the smell, rather than in response to its chemical structure.

Waite: What about the relationship between olfactory function and sexual function?

Lindau: Older women have reported to me that part of the reason that they don't feel interested in sex is that they don't smell and they don't taste. Also, abnormal body odor has an effect. So, inability to smell and unpleasant smells can limit social and sexual interaction.

McClintock:

You raise the important issue of the social and sexual function of odors. A study of older adults is an excellent opportunity to take what is now known among young adults and look at how it maps onto processes of aging. The measures that I've talked about so far are well-studied and commonly used as indicators and correlates of olfactory function, but are only applied to the context of the physical world.

Rachel Herz at Brown University has studied sexuality in young adults and found a profound sex difference; olfaction and, to some extent, taste are the most important sensory modalities for women, while vision is the most important sense for men, on average. When we consider this sex difference along with the fact that smell is one of the first senses to diminish with age, we can identify important research questions about the social and sexual roles of olfaction.

Let me emphasize that when we talk about "body odors," we are often talking about "body scents" as well. Mostly, it is the faint smell that is found at the nape of the neck or left on a pillow. Many of us can recognize these scents of persons important to us, but when they are presented by themselves, isolated, we don't recognize them as being human scents. We could brainstorm about how to put together a test of a range of stimuli with natural body scents, to see whether people can detect them and what is their emotional reaction to them.

We have studied effects of very low concentrations of specific steroids, such as androstadienone, which modulate cortisol and the autonomic nervous system, without being detected as an odor. They are well below conscious detection. These compounds take about 10-20 minutes to take effect, and are subliminal. It would be interesting to test and then re-test about 20 minutes later to start to understand the psychosocial and emotional reactions these compounds produce. In studies of young adults, there are striking individual differences and sex differences in emotional reactions to these natural social chemosignals.

Lindau:

From the phenomenological side, it would be quite interesting to outline the relationship between olfaction and taste and social and sexual function, and how these relationships change as people age. But, from the intervention side, the idea that modulating taste and smell ability could improve social and sexual function for older people is very compelling.

Furthermore, the differences between the importance of visual and olfactory signals for women and men at younger ages would be interesting to explore in an older population. As men age, their sexual response cycle comes to look more like women's response cycle. So, perhaps olfaction and taste also become more important for men. Thus, there is a compelling reason to look into these in both genders.

Levinson:

What is the relative importance of sensory function, as compared to hormonal levels?

- McClintock:** For example, hormones change what is salient for a given sensory system. At the same time, they increase sexual motivation. In order to compare these effects, you need large sample sizes, and a population-based sample is an excellent opportunity to evaluate this. But, you can't simply do an analysis of variance, because these elements are all interconnected.
- O'Muirheartaigh:** The measurement of this seems extraordinary difficult, and it seems that this introduces an interviewer effect that we haven't thought about before, which is how the interviewer himself or herself smells. Also, this points to the issue of smells in particular homes when we consider household-based interviews.
- McClintock:** If you're interested in pursuing this, it's not as difficult as you think. It is already established that scents collected from people at different stages of life have different emotional effects. For example, Denise Chen has demonstrated the scents of older adults can be comforting.
- Lindau:** What about habitual smells versus clinical measures of function? For household surveys, a critical issue would be whether elements of the home environment should be controlled or measured.

Biomarkers and Medications – Todd Semla

Medication use can potentially impact everything that has been said already at this workshop. Ninety percent of patients over 65 years of age are taking at least one over-the-counter or prescribed medication. Many people are taking more than just one medication – the average for adults over 65 years old in a community-based population is four to six medications per day.

Medication use is not a true biomarker, but it is a marker of disease. There are specific dyads that tell you a great deal about a person's health. For example, a person taking cholinesterase inhibitors likely has Alzheimer's disease or some other form of diagnosed dementia. Similarly, a person taking an antibiotic probably has some sort of infectious disease, and insulin use signals diabetes.

Medications can impact or control biological functions, such as blood pressure, heart rate, and blood sugar. They can certainly have an impact on sexual function, whether they are used to treat sexual problems or if their side effects include sexual impairment. Medications are associated with increasing risks of certain syndromes, particularly in the geriatric population. Finally, drug interactions are also a concern, particularly as people take several medications to address a number of problems.

It is important to think about how medications will be defined in a study. Will you limit the definition of medications to prescription drugs, or will you include over-the-counter medications, vitamins, and herbal medications? Often, when you ask people about medications, they don't think about things like aspirin, which their doctor doesn't prescribe.

When collecting information about medications, it helps to ask the respondent to take out his medications before the interview. It can take a lot of interview time if a person has to go through their house – to the kitchen, the bedroom, the bathroom, and so forth – to collect all of the medications that he uses.

In terms of recording information on medications and entering it into a database, you can collect broad information or you can collect very specific information. The options range from noting that someone takes a cardiovascular-related medication, which is not very useful, to recording that they're taking a statin to lower their cholesterol. To get more specific, you can look at the ingredients in the product. What generic version are they taking? Which aspirin? Which ACE inhibitor? Finally, you can be even more specific by recording the strength and the dosage and asking whether a person is taking it as prescribed and, if not, how they are taking it.

Medication use can also be measured in serum and saliva. When interviewers are not health care professionals, they probably aren't familiar with a lot of medication names. There may be situations where bottles are unlabeled, the respondent is using samples, or he or she has discarded the medication container. All medications have markers on them, and if the interviewers are trained to record whatever information they can get (which might include, color, tablet, and letters and numbers on a capsule), various computer programs can be used to identify the medication later.

It is very important to ask the person about the purpose of their medication. If the person, for example, is taking a beta-blocker, it helps to ask them why they take it because it could be used to treat blood pressure, tremors, or migraine headaches. In 95 percent of prescription medications, the reason that a patient gives for taking the medication is not the most common reason for which the

particular medication is prescribed. For example, when asked about things like anti-depressants, respondents commonly explain that they are using the medication “for energy.”

Data entry and data management of medication logs are time-consuming. The data from the Established Populations for Epidemiologic Studies of the Elderly (EPESE) in Boston comes from pharmacists, but most studies won’t have that luxury. Researchers need to find ways to use numerical codes for medications and to make the information as accessible as possible. Computer-aided techniques, such as programs where the interviewer can start to enter the medication name and options pop up on the screen, can be very useful.

Finally, note that medications can affect other things that we have talked about, such as taste. Loss of one’s sense of taste is a common complaint after beginning a new medicine.

Halter: What about when you have couples who share medications?

Semla: You have to ask about shared medications.

O’Muircheartaigh: Will prescriptions have a bar code that might help us?

Semla: Prescriptions probably will not have a bar code. Prescription drugs aren’t standardized to my knowledge. Unless UPC codes from over-the-counter medications are standardized, I don’t see how this would be possible.

You also have to make a decision about what time frame you’re interested in. Do you want to know what medications respondents have ever taken, or what medications they have taken in the past year, or what medications they are taking now?

O’Muircheartaigh: Did you say that there is a coding database that we could use?

Semla: There is a medication-coding database called “Drugbook,” but it is a large file. It used to be publicly available from Minnesota, but I’m not sure if it is now.

Halter: I would like to return to the issue of disease versus subtle changes brought about by natural aging processes. Considering that many people will be on many medications, it seems that it might be difficult to identify subtle aging effects, when we can be overwhelmed by disease and the proliferation of medications.

Semla: If you’re looking for an aging effect, it might be fairly small compared to the effect of something like diabetes.

Lindau: This is why longitudinal design is so important. A three-year interval, for example, allows the identification of more subtle aging processes, such as cognitive decline, changes in sensory function such as smell and taste, and overall physical health.

Biomarkers of Immune Function – Thomas McDade

Population-level research on immune function has lagged behind advances in measuring cardiovascular disease and nutritional intake in population-based samples because there are few minimally-invasive methods that are sufficient for measuring immune function. Most measurements of immune function require the collection of large volumes of blood, the culturing of cells, and the immediate analysis of samples. These requirements are not easily accomplished in household situations.

There are, however, a few options. First, saliva samples offer some insight into immune processes, such as secretory immunoglobulin A (sIgA), in particular, and other measures of immune system activation. However, these measures provide more insight into localized, mucosal immune activity rather than central immune processes.

A second option is the collection of whole blood through blood spots. There are two measures developed to test immune function through the analysis of whole blood, both of which have been validated in my research. The first of these is testing for antibodies against the Epstein-Barr virus (EBV), to which about 90 percent of an older population would have prior exposure. This testing procedure builds on early work in psychoimmunology which relies on the ubiquity of exposure to Herpes viruses. You can measure antibodies against the virus as an indirect measure of cell-mediated immune competence, an aspect of immune function that is critical to maintaining the virus in its latent state.⁶

EBV antibodies have been shown in the psychoimmunology literature to be among the strongest and most consistent correlates of chronic stress. The specific physiological pathways have not all been worked out yet, but it is one of the best immunological measures of chronic stress and it has been used successfully in a number of population-based studies.

The second measure in blood spots is C-reactive protein (CRP), which is a good measure of cardiovascular disease risk. Cardiovascular disease has recently been reconceptualized as, in part, an inflammatory disease. Levels of CRP which were previously thought to be normal are now being identified as predictive of cardiovascular disease risk across populations.⁷

Other whole blood measures that might be of interest require blood smears on a slide that can be used for a cell blood count and differential, which is a basic clinical measure. You can also use immunofluorescence to quantify CD4 and CD8 lymphocytes, which might be interesting, particularly in the context of aging. There are validated blood lymphocyte cultures, which require venous blood spun down and then incubated with a mitogen. Some people argue that whole blood is a better medium for culturing lymphocytes because that is the milieu in which lymphocytes typically circulate. There are some protocols that use a small volume of blood by simply pricking a finger, collecting it in a capillary tube, and transferring it to a pre-prepared vial. You could conceivably measure lymphocyte activity this way, but it would require a great deal of coordination and infrastructure to validate this.

⁶ McDade, T.W., Stallings, J.F., Angold, A., Costello, E.J., Burleson, M., Cacioppo, J.T., Glaser, R., and Worthman, C.M. (2000). Epstein-Barr virus antibodies in whole blood spots: A minimally-invasive method for assessing an aspect of cell-mediated immunity. *Psychosomatic Medicine* 62:560-568.

⁷ McDade, T.W., Burhop, J., and J. Dohnal (in press). High sensitivity enzyme immunoassay for C-reactive protein in dried blood spots. *Clinical Chemistry*.

The third possible option for biomarker collection is the vaccine challenge. You could provide your participants with a flu vaccine, which is recommended by the Centers for Disease Control (CDC) for older Americans, and then you could measure the antibody response to that vaccine a few weeks later. This is a nice integrative, functional measure of immuno-competence. Of course, this procedure is more invasive. It would require someone trained to administer the vaccine, or the respondents would have to visit a clinic to receive the vaccine.

Part III: How Can Biomarkers Be Collected in a Population-Based, Household Survey with Non-Medical Interviews?: The Add Health Experience

Richard Udry

One of the most interesting experiences that we have had with the Add Health collection of biomarkers has been measuring in women levels of human chorionic gonadotropin (HCG), which is a diagnostic hormone correlated with pregnancy. With this, we were first to document non-clinical laboratory pregnancies and compare these pregnancies to survey data, including both reported sexual activity and pregnancy termination. While determining pregnancy might not be a useful endeavor among older populations, it might be useful to measure sperm count in urine collected from females. This can be a good marker of sexual activity and can be used to document whether women are accurately reporting their sexual activity.

Biomarkers have been very valuable in the Add Health study and all of my research since Add Health has included the collection of biomarkers. We have had great success with it, even though people were skeptical at first and thought that we wouldn't get accurate samples. Add Health is, by far, the largest current biomarker operation. With the 2001-2002 sample, we collected biomarkers on 15,000 young adults ages 18-24. While each of these biomarkers has its own logistical challenges, the outline of the work is surprisingly routine.

One of the most complicated aspects of biomarker collection is laboratory security. Add Health has an elaborate security system, which complicates record keeping and biospecimen collection. I think that one of the most difficult challenges brought by biomarker collection is designing a security system. Any research project needs to include security considerations with planning for biospecimen collection. The major security threat is data intrusion. Biospecimens yield will have a great deal of sensitive data, and many of the respondents will have partners who are interested persons in your data. These partners are potential intruders. But many other people are potential intruders, as well, and people do try to access data. Data protection is necessary because most respondents won't want anyone else to have the data obtained from their biospecimens. These security issues add complexity to biomarker collection.

There are also several issues particular to the collection of biomarkers in older Americans. First, there are potential differences in motivation, when compared to the collection of biomarkers in younger adults. In Add Health, for example, people who had no sex partners were likely to refuse our request for biomarkers to measure STDs. If respondents didn't think that they were at risk for something, they were more likely to refuse its collection. Add Health gave individual incentives for each of our biomarkers, except for DNA collection. For the DNA collection, we got 85 percent participation from our respondents, but for all of the other biomarkers, we got 95 percent participation. We gave individual incentives of \$10 each for the specimens and \$10 for participation

in the study as a whole. (We had separate consent forms for this.) There was an additional bonus for recruiting your partner for the study. In the end, this has amounted to a lot of money.

Second, biomarker collection often causes unanticipated problems. For example, we used mouthwash solution where each respondent was supposed to screw the top off of the bottle, put it in his mouth, and then put the top back on the bottle. A woman called and said that she didn't do the mouthwash because she wasn't confident that the solution on the screw cap bottle was sterile and safe for her to put in her mouth. You need to anticipate things like this as much as you can.

Another problem that relates to older respondents is the sensitivity and specificity of the tests themselves. When population rates are very low, false positives can outnumber true positives, so you need to think seriously about whether the test is worthwhile and whether or not you will inform your respondent about their results. For example, let's assume that the sensitivity of a test for gonorrhea is 97 percent and the specificity is 98 percent. If the true prevalence of gonorrhea in the population is 1 in 100, for every three positive tests, one will be a true positive and the two others will be false positives. If the rate in the population is 1 in 1000, then one will have gonorrhea and 19 will be false positives. As a result, you would tell 19 people that they have gonorrhea, when they don't actually have it. You need to be sensitive about the potential of false positives and the effects that they have on the population and the individual respondents. There is no solution to this problem, because the tests weren't designed for population-based testing – they were designed for clinical use. This is an ethical problem that you need to consider.

There are some other, more general logistical problems with biomarker collection. First, logistical problems may arise with the sample collection. Our tests for chlamydia and gonorrhea were LCR tests, which actually measure the presence of DNA for the two organisms. People could tell us whether they were ever exposed, but we were more concerned about whether they currently had these diseases. However, the optimum conditions for testing for these are very stringent. The main problem was getting too much urine. We wanted a first catch urine, when a respondent hadn't urinated for over an hour. But if we got too much urine, we wouldn't get enough organism. So we put a line around the bottle at 15, although we were prepared for 20. Both men and women had a hard time limiting the amount of urine that they gave us. Additionally, the specimens often arrived too warm. The urine sometimes took too long to arrive, and so it got old. September 11, 2001 fell in the middle of our data collection, which also delayed the arrival of many specimens.

Another logistical problem is notification of results. We notified respondents about their results through an anonymous mechanism, so that we didn't know who we were notifying. After a complicated change of identification numbers, respondents were given a hotline number and their identification number so that only they could get their information. We phoned a random sample of people plus all of those who tested positive for HIV to check whether people had gotten their test results and asked how we could help them to access their results. Our technique was pretty good on paper, but only 25 percent of the respondents called and got their results. We only got about an additional 10 percent of the respondents to check their results after the follow-up call, so it is very hard to get a higher rate.

Cohen: Perhaps older adults will be more likely than adolescents to want to access their results. Is there an ethical obligation to tell respondents everything that was measured, even when some measures are not clinical measures that have a definitive meaning for the respondents, such as C-reactive protein?

Greenland:

I'm on the advisory board for the Framingham Heart Study, which is about a 50-year-long population study of heart disease predictors in a sample of people living in Framingham, Massachusetts. The policy of the study for a long time was to take measurements and when those measurements were not known to be predictors of anything, they were not reported to the respondents. In the initial years of the study, there were very few results reported to the respondents. As certain things started to become known predictors, like blood pressure and cholesterol levels, those things began to be reported to participants. Other things, like inflammatory markers, which are considered to be investigational, were not reported to participants at all.

The consent form clearly states that this is not clinical medicine, it is research, so anything known to be clinically relevant would be reported to them and anything not known to be clinically relevant would not be reported to them. In recent years, they have added a new measure, the heart scan, which is not necessarily known to be predictive of disease outcomes, but it is being used in the public domain for supposed prediction. The researchers were interested in doing this to see how results from the heart scan correlate with other known biomarkers, and to see if the heart scan would provide additional information. They added to the consent form that the heart scan is known to be experimental and would not be reported to the participants.

However, the IRB refused to let them exclude the heart scan results from reporting, for several reasons. First of all, while the heart scan is not known to be predictive of disease outcomes, its results often trigger clinical intervention. The researchers are therefore no longer studying the natural history of the disease – they are now studying the modified history of disease, based on the measures that they've instigated. In addition to that, the heart scan, in particular, also scans the lungs. About 50 percent of people who have heart scans find that they have something in their lungs that looks suspicious, but it is difficult to investigate. The only way to find out if it is something of concern is to watch it or to biopsy the lung. We could have made the decision not to analyze results regarding the lungs, but then we would have run the risk of litigation if someone developed lung cancer and we had the data and didn't look at it.

Cohen:

But those rules were created in the 1950s, and we are living in a different world now. It can be argued now that the respondent has the right to know about anything that you measure that could have some clinical implication. Even when something is clear, like testing for STDs, you face federal reporting laws. I think that there is no biomarker that you can measure that a respondent doesn't have a right to know.

Greenland:

These are complicated problems. Even if you do research in China, you have to follow the American IRB rules. If you take money from some American institution, the same rules that apply here apply there.

Part IV. Next Steps: Strategies and Infrastructure for Collecting Biomarkers and Biometrics in Domiciliary, Population-Based Health Research Involving Older Adults

Moderator: Linda Waite

Discussants: Myron Cohen, Thomas McDade, William Parish, Parminder Raina, Teresa Seeman, Richard Udry

Waite: Following from the last section, this part of the discussion will continue to focus on things like infrastructure and logistics that should be considered in the collection of biomarkers.

Cohen: If you watch crime shows on television today, you can learn a lot about biospecimen collection and how these specimens are handled by forensic investigators. Investigators have to figure out how to overcome hurdles regarding collection and conditions. Don't underestimate the literature on how biomarkers have been collected badly in the past, such as the urine collection program that Udry talked about. We talked to NHANES about how they addressed problems of urine collection, and they said that the simply distributed the urine into separate tubes, but that is not a good way either. Specificity and sensitivity are known for clinic-based collection, but these procedures are modified when specimens are collected in the field.

Lindau: Regarding the ethics of reporting results, can respondents give informed consent that relinquishes their ability to access the results of the data?

Cohen: It's possible, but a separate consent would be required for every test performed.

Seeman: Sometimes the availability of information from the testing procedures actually helps to motivate respondents to give biospecimens. People want to have the results and take them to their doctor. Their doctor will then probably say that he or she doesn't know what to do with the results and will run further tests. But, part of the reason that people agree to the samples is that they want the results back.

Cohen: In these days, an IRB would probably not approve not telling the respondents.

Leitsch: Is it possible to filter these results by giving them directly to a respondent's doctor, or does that violate privacy?

- Cohen:** HIPAA laws are very dense. Although the client is telling you what pills he is taking, if you collect the data and tell this to someone else, your informed consent must address the HIPAA laws. You are violating HIPAA laws if you tell someone else without consent, even if it is the doctor who prescribed the pills. You need to think about this particularly with the collection of information on medications.
- Seeman:** One of the ways that we dealt with it for the Study for Women's Health Across the Nation (SWAN) was that if people had values that raised some concern, we'd suggest that they share the results with their physician. We also had a physician on staff to address values that were in critical ranges.
- Waite:** Some of the tests regarding immune function, endocrine function, blood pressure, height and weight, vision, and smell seem pretty safe.
- Seeman:** The practicalities and safety issues around collecting biomarkers are complex and will be amongst your biggest challenges. However, the question of whether and how to provide any results to participants is an equally crucial issue that should be addressed.
- Cohen:** The bigger questions surround what is worth learning. You need to think through your hypotheses and really target your biomarkers to get the information that will be useful. Storing things is good because that's how we learn things 20 years from now about disease development, but it's hard to know what to collect and save without specific hypotheses. Secondly, sensitivity and specificity of many tests are terrible and have little meaning. Be careful about what you measure and how you use the results.
- O'Muircheartaigh:** In terms of specificity, if you're carrying out population-level analyses and you're looking for correlations between certain measures and others, the standards are lower than if you are clinically-driven and you want to know whether a particular individual has a particular disease.
- Parish:** But, for the notification requirements, you're suddenly clinically-driven.
- Cohen:** It's a catch-22 – with some of these measurements, you're actually studying the measure's sensitivity and specificity in the population. For example, we know that antibodies wane as people get into their 60s, 70s, and 80s. Predictably, a substantial number of older adults will not have pneumococcal antibodies. We might have them today, but we won't 20 years from now. We know a lot about pneumococcus and the elderly, but for many things, you are actually studying the things that you think you're using as a biomarker. If there are no clinical tests available for some of your markers, you are actually studying the sensitivity and specificity of something that has been thought to be the gold standard in the clinical setting. The way that you would do this is to draw a tube of blood and do the analyses, and then use information about the person's condition to test a second tube to verify positive results.

- Lindau:** If we use biomarkers to get a more robust picture of health at older ages, should we use a few tried and true biomarkers and/or should we focus on markers that are relatively new discoveries that we could be testing to give us new information and move toward new discoveries?
- Waite:** In a typical social scientific study, people themselves are asked to report about their health and disease states. For example, in the Health and Retirement Survey of 20,000 people, we simply asked people whether their physician had ever told them that they have cancer. Or, we ask people to rate their health. Social scientists have relied on data collected this way for years, but people in the medical sciences place no value in these measures. Many people don't know what they have or don't understand what they were told by their physician. We can benefit by having additional measures of health and disease and being able to identify, say, the five most prevalent diseases in the elderly. We can ask about diabetes, hypertension, obesity, cognitive decline, cancer, and depression, among others. We could then go back to these people three years later to see what their trajectory is. If we have multiple measures of disease states, we could, for example, say that people who have strong intimate relationships show better trajectories.
- Cohen:** Most of the validation in social scientific studies has been done by biomarkers – specifically in areas like alcohol and drug use, STDs, and sexual promiscuity. But, you're not trying to validate social scientific measures, you're talking about showing that many people may not know the true state of their health.
- Lindau:** It's also about trying to identify pre-diagnosed disease.
- Udry:** You want a measure that you can evaluate against other measures and decide which the right one is.
- Waite:** We can use a latent-factor model to combine measures and find the best one. Udry: In Add Health, we asked people whether a nurse or physician had ever told them that they have HIV. We had about a dozen people who said yes to this, but none of them came out positive on HIV. Wouldn't you think that people would get this right? So, we tested these people again, but all of those were negative. Now we have three pieces of information and have to decide which one to believe.
- Cohen:** This could be an issue of the interviewer keying the wrong button. Or, the respondent was misleading you.
- Laumann:** Or, they were told something by their physician that they shouldn't have been told, and the doctor should be sued.
- Cohen:** You can look at the socioeconomic status of these respondents and how old they are, among other factors, and you should be able to predict with some accuracy why this happens.

- O’Muircheartaigh:** There are some pieces of the data that are simply not salient to people. There are always small numbers of people who give information that does not match the rest of the information. Measurement error is universal and any data that does not have measurement error is falsified.
- Parish:** Many of the same issues that you have mentioned were seen in our study in China. We had high compliance. In fact, compliance was so high that we ran out of urine bottles.
- We couldn’t use a telephone system so we unfortunately had to use self-addressed envelopes and a coded insert for positive or negative results. Less than half of the people elected to be notified, so many of our respondents never received their results. We didn’t find a huge problem with false positives.
- Udry:** You’ll get too many false positives on any STD that you test for.
- Cohen:** Infectious diseases are the worst worry for false positives. Things like testosterone level are not a problem.
- Udry:** If you’re testing for HIV, you have to particularly worry about the, say, four cases where you identify measurement error on HIV. But, you have to ask if a medical practitioner has ever told you that you have X or Y. Those are validated questions that have been asked on virtually every national survey about health. Sure, there is measurement error, but they are highly predictable and highly useful. I don’t know that you need four indicators of diabetes, because you have a large agenda and collecting every disease indicator possible means that you are going to compromise on other parts of your agenda. There are a lot of possibilities here, but at the end of the day, you need to come up with a short list and some of the more basic and cost-effective approaches are going to be just fine.
- Cohen:** There is an issue, though, when you start a longitudinal study with particular indicators and belief systems about tests. Perhaps you want to measure prostate-specific antigen in men. What does that mean the day you start the study and the day you finish? With Add Health, Abbott Laboratories cancelled some of the lab tests that they would do for certain things. There are therefore clinical issues that also come into play.
- Parish:** Another logistical problem with the laboratory is labeling the identification numbers on the samples. We had handwritten identification numbers on the samples and many of them came off or were washed away.
- Cohen:** A commercial laboratory will probably charge you too much for these tests, but you need a CLIA-approved laboratory. The assays differ from lab to lab, so all samples of a particular assay have to be conducted in the same laboratory, or your measurement may not be consistent.

McDade: There are some logistics regarding the collection of blood samples. There are clearly two perspectives here: the clinical and the population-level. You don't have to choose to collect specimens that are directly related to particular clinical outcomes for them to be of interest. You can study things that might significantly affect behavior, like testosterone level, but that may not have a clear clinical relevance. This is why population-level research using biomarkers has been so useful in the past.

If you choose to collect blood, the first decision is whether or not you want to collect plasma. Plasma collection requires a phlebotomist. If you want to collect whole blood, you need to think about whether you will use filter paper, a capillary tube, or portable instruments that interviewers will bring to the interview site, like a Cholestech for glycosylated hemoglobin or lipids. If you do blood spots, those samples need to be dried for a couple of hours before they are sealed. This does not necessarily have to be done at the interview site. Training the interviewers to collect the blood is easy. The costs for the blood collection devices are about \$1 per sample. For analysis, EBV antibodies are about \$5 per sample, high sensitivity C-reactive protein is about \$3 per sample for the reagents (not for the labor). This is fairly inexpensive, and probably cheaper than plasma.

Cohen: A good example is testosterone because that is something that a 70-year-old man would be interested to know. There are so many messages in the media about what testosterone levels mean.

McDade: Yes, you should report the result because it has meaning for the respondents, but its clinical relevance is not clear and it may be most related to non-clinical outcomes, such as sexual activity and mood. There are multiple agendas here. The population agenda is most important to this project, but you also have to attend to the clinical relevance of things.

Seeman: In returning to the issue about whether it is useful to stick with tried-and-true traditional tests or to test out new indicators, it seems that part of your goal is to get biological parameters that will give you an alternate view of the more traditional self-report measures. Perhaps you should emphasize some of the more standard measures like glycosylated hemoglobin, which can be related to diabetes, and something for inflammation and lipids. But, maybe you should also consider something that is more linked to parameters regarding sexual function.

Blood pressure, waist parameter, and height and weight would be on a short list. You could also look at things like glycosylated hemoglobin, CRP, and lipids (cholesterol, HDL, LDL, and triglycerides) from dried blood. Your purpose in this case seems to be classification in terms of relative levels across a cohort of people, and you may get enough window and it may be feasible within your constraints.

Laumann: What about indicators of stress?

- Seeman:** Spot samples can tell us about stress, but they are very hard to collect. It's difficult to start all interviews early in the morning, but this is when you want to collect specimens like cortisol. Time of day is also a problem, and very few people have made efforts to normalize biomarker collection across the time of day. Another issue is that peoples' diurnal cycles may not be the same, which further complicates decisions regarding when to draw single samples. It is not invasive to test cortisol through saliva, but you need five measurements throughout the day, and this is difficult to get respondents to comply with because it's a larger burden.
- Laumann:** If we want biological measures that can be correlated with social experiences and attitudes, such as happiness or friendliness or quality of life, how could we best index these things biologically?
- Seeman:** There is a great deal of methodological work that needs to be done, perhaps using subsamples that could be brought in to undergo more clinical work. This would help us understand things like the effect of the home environment and what it means to get cortisol in the morning. We don't actually know what the diurnal rhythm means in terms of cortisol fluxuation and its relationship to health outcomes. We therefore need to do more methodological work to determine the minimal protocols that could be used in communities to link actual life experiences to biological measurements.
- Cohen:** Do you think that cortisol is a valid measure, since we don't really know what it means and what parameters are normal in particular situations?
- Seeman:** We do know what salivary cortisol "means" – methodological work has shown that it is a valid marker for plasma/blood levels of free cortisol. And, there is considerable research linking cortisol to various health outcomes (not surprising since cortisol is one of the central "elements" of the HPA axis, one of the major regulatory systems of the body).
- Levinson:** What should float to the top for a short list for biomarkers – based on feasibility and usefulness? Perhaps there are some measures that are less feasible, but would be worth pushing to do because of their potential usefulness? Or, some areas, like the olfactory measures, that are less established but could help us to make new discoveries about health and aging?
- Cohen:** If older women will provide self-administered vaginal swabs, you can learn about trichomoniasis in a population and how it affects quality of life. HPV and herpes will also help to inform you about sexual health among older women. This would definitely advance science – you would learn something that no one knows. But, I don't know if older women would tolerate this.

Lindau: From a clinical perspective, and dealing with older adults and sexuality issues, the vaginal discharges and odors are critical. By getting a population-based idea of what the vaginal mucosa look like, we can get a wealth of information about propensity for infectious diseases and hormone levels. This is a discussion that is often in the media, too, about hormone replacement.

Olfactory function is also important, as well as visual function and hearing. There are very important hypotheses about how these physical functions are related to social and sexual functioning and health.

Levinson: What should be on the short list?

Lindau: What if you had the opportunity to go into the homes of older Americans, ages 57-84, using your expertise about older adult health – what biomarkers would be at the top of your list?

Seeman: Blood pressure, waist-hip-ratio, height/weight, glycosolated hemoglobin, lipids, CRP.

McDade: Testosterone – particularly if sexuality is an interest, and it's easy to measure.

Raina: Important functional measures might include hand grip, vision, and hearing. Walking and climbing stairs are good indicators of physical activity. Blood indicators, such as protein levels and glucose tests, are useful. HbA1c (glycosylated hemoglobin), urine, amyloid, and Vitamin B, are commonly used.

Halter: Other studies of older populations that focus on biomedical issues have a longer list. What other studies don't have are details regarding sexual function. I would measure blood pressure in the foot (in addition to the arm) to get the ankle-brachial index. This provides an indicator of peripheral vascular disease, which is likely predictive of erectile dysfunction.

I would probably measure electrical impedance and CRP. CRP correlates with smoking, obesity, physical inactivity, hypertension, and diabetes. It's an integrated function of immune and inflammatory activity, and it has pretty good measurement characteristics.

I would run a 60-second EKG, because then you can actually calculate things like heart rate variability and it is completely non-invasive. You don't have to report any illness because you don't have a full EKG, just a 60-second rhythm strip, which gives you some estimate of autonomic function.

Waite: Could a non-medical person be trained to do this?

Greenland: Yes. Non-medical people do this in a clinical setting, so you could likely train interviewers to do this.

You might also want to consider a matrix of hypotheses and then have possible measures and consider which are most valid, cost-effective, and convenient.

Cohen:

Because there are a great deal of biomedical studies of elderly people, the advantage of using biospecimens to inform social scientific research comes from the hypotheses. Let your assays be informed by your hypotheses and what you really want to learn and contribute.

APPENDIX A
Synthesis of Scientific Disciplines in
Pursuit of Health: The Interactive
Biopsychosocial Model

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SYNTHESIS OF SCIENTIFIC DISCIPLINES IN PURSUIT OF HEALTH

the Interactive Biopsychosocial Model

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ABSTRACT Twenty-five years ago, George Engel proposed a challenge to the biomedical model and its limited view of disease as biologically rooted. Building on Engel's work, we present the Interactive Biopsychosocial Model (IBM). The IBM argues for a reorientation in biomedicine where research, education, and clinical practice: (1) address health in addition to illness; (2) aim to decipher interrelated biophysical, psychocognitive, and social processes in health and disease, rather than seek a single root cause; and (3) take into account the social networks of the individual to achieve, maintain, and maximize health and well-being for individuals, their significant others, and society. Based on an interdisciplinary collaboration of medical and social scientists, this paper demonstrates the application of the IBM to understanding and generating

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hypotheses about the longitudinal relationship between sexuality and health, and sexuality and chronic illness (diabetes mellitus) at older ages. The model provides a dynamic, dyadic, framework for building scientific hypotheses about the etiologies and consequences of health, well-being, and disease throughout the life course.

The dominant model of disease today is biomedical, and it leaves no room within its framework for the social, psychological, and behavioral dimensions of illness. A biopsychosocial model is proposed that provides a blueprint for research, a framework for teaching, and a design for action in the real world of health care.

—George Engel (1977)

The time for this larger synthesis of scientific disciplines in pursuit of human health has come.

—National Research Council (2001)

IN 1977, GEORGE ENGEL, professor of psychiatry and medicine at the University of Rochester, proposed integrating psychological and social variables into prevailing models of disease, and created what he called the “biopsychosocial model.” Now, a quarter of a century later, the National Research Council and the Institute of Medicine (IOM) are urging scientists to integrate psychosocial and behavioral processes into attempts to decipher pathways of disease, health, and well-being, and to include biological measures in population-based social science research (Finch, Vaupel, and Kinsella 2001; IOM 2001; National Research Council 2001). This call for integrative approaches is driven in large measure by the increasing prominence of psychosocial issues in clinical practice and education. For example, physicians are often confronted with patients who cannot afford regular checkups or medicines. Older patients experiencing cognitive decline may have difficulty adhering to directions on prescriptions, and patients who have spouses in poor health may be less able to manage their own chronic illness. To promote the cross-disciplinary collaboration necessary for a new approach to the science of health, we need a unified vision of health and disease.

In this paper, we examine the theoretical foundations and limitations of disease-oriented models of biomedicine and propose a new model, the Interactive Biopsychosocial Model of health (IBM). Based on Engel’s work, the IBM argues for a reorientation in biomedicine where research, education, and clinical practice: (1) address health in addition to illness; (2) aim to decipher interrelated biophysical, psychocognitive, and social processes in health and disease, rather than seek a single root cause; and (3) take into account the social networks of the individual to achieve, maintain, and maximize health and well-being for individuals, their significant others, and society. The model provides a dynamic framework for building scientific hypotheses about the etiologies and conse-

quences of health, well-being, and disease throughout the life course, and it can be used, in addition, as a teaching tool at the bedside or in the classroom.

This work arises from our research in aging and human sexuality, where the greatest scientific and clinical challenge is as often understanding and maintaining health as it is rectifying dysfunction or disease. Additionally, research in sexuality demands a shift in focus from the individual to the dyad or larger social network. The IBM emerged as a framework for scientific investigation about health and life quality over the life course, when it became apparent that we would need to incorporate psychocognitive and psychosocial variables into traditional disease-oriented models. Below we describe this new model and apply it to the relationship between aging and sexuality.

HISTORICAL CONTEXT

In proposing the biopsychosocial model of disease, Engel (1977) issued a “challenge for biomedicine” to reconsider the prevailing biomedical model of disease. The biomedical model, still the dominant framework guiding medical research, education, and clinical care today, focuses on the root cause of disease, where disease is “fully accounted for by deviations from the norm of measurable biological (somatic) variables.” Engel offered, instead, a model designed to “provide a basis for understanding determinants of disease and arriving at rational treatment patterns of health care.” Engel’s groundbreaking work grew out of his clinical psychiatric practice, where he found himself often frustrated by “adherence to a model no longer adequate for the scientific tasks and social responsibilities” of medicine. He aimed, therefore, to change the profession’s approach to the causes of illness and disease, and to widen the framework for the clinical approach to illness, in general, and mental illness in particular.

General systems theory was emerging in both the biological and social sciences during the formative years of Engel’s work, and Engel used this theory to lay the groundwork for his biopsychosocial model (Buckley 1967; Henry and Stephens 1977; Parsons 1951; von Bertalanffy 1968). Engel claimed that “systems theory holds that all levels of organization are linked to each other in a hierarchical relationship so that change in one affects change in the others,” and that this theory treats “sets of related events collectively as systems manifesting functions and properties on the specific level of the whole.” Engel believed that applying systems theory to medicine could reconcile two fundamental tensions implicit in the traditional biomedical model: mind-body dualism, the belief that the mental and the somatic operate independently; and the reductionist-holistic dichotomy, in which complex phenomena are derived from a single physical aberration from the norm rather than from an integrated system where changes interact at various levels.

While Engel’s work consciously shifted away from the primacy of biological etiology, he remained focused on the individual as the embodiment of a disease

and its consequences. The treatment of disease was still framed in the clinical setting and conceptualized primarily as an interaction between physician and patient. Social variables, only superficially described, became simply additional characteristics of the diseased individual to be considered in the pursuit of the root cause.

Although Engel's work is widely cited in the medical literature (a citation search in the Web of Science Citation Index found 1,419 citations of the *Science* article as of June 2002), the model remains largely on the margins of biomedicine, particularly as a framework for scientific investigation. Engel's model has failed to replace the biomedical model for two main reasons: clinicians and scientists continue to emphasize the progression from etiology to disease to the exclusion of health as an outcome; and professional and research institutions are often structurally rooted in the biomedical model. These factors motivate us to reconsider the utility of the biopsychosocial model for defining health. In the following sections, we offer a framework for integrating the social factors that influence health, wellness, illness, and disease into the clinic or the science of medicine.

DEFINING AND MEASURING HEALTH

Historically, a negative definition of health has prevailed in biomedicine: i.e., health is the absence of disease, dysfunction, or injury. Epidemiologic measures assess population health by rates of morbidity and mortality. Both perspectives rely on normative judgments about the average health of individuals in a given clinical population, community, or society. The primary appeal of these definitions lies in ease of measurement (e.g., measurement of blood pressure, or observation of death certificates), but outcomes in these models are limited to physiological endpoints. Positive outcomes, such as quality of life, well-being, or resilience, typically lie outside these definitions (IOM 2001).

The demographic shift in the age of the U.S. population (Kinsella and Velkoff 2001), combined with medical advances resulting in increased longevity, provides additional impetus for a new, more holistic approach to aging, health, and adult human development. Longer, healthier life in industrialized nations requires a shift in focus from treatment to prevention, from reduction of mortality caused by acute illness to reduction of morbidity due to chronic illness, and from the management of external threats (injury, infection) to the modification of internal threats (negative behaviors such as smoking, poor diet, or sedentary lifestyle). Concepts of successful and productive aging incorporate a positive behavioral orientation and a perspective that encompasses the entire life course (Bass and Caro 2001; Rowe and Kahn 1997). Building on these concepts, the IOM (1998, 2001) proposes "positive health," defined as "a healthy body; high-quality personal relationships; a sense of purpose in life; self-regarded mastery of life's tasks; and resilience to stress, trauma, and change."

Health is a “multi-attribute concept” that depends upon a complex network of physical, biological, environmental, economic, social, cultural, and possibly metaphysical (spiritual and moral) factors (Cutler and Richardson 1998; Thorsen and Harris 2002). The World Health Organization (1958) defines health as “a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity.” On a population level, the definition of health evolves with social change: “The rising expectations of the past 150 years have led to a shift away from viewing health in terms of survival, through a phase of defining it in terms of freedom from disease, onward to an emphasis on an individual’s ability to perform daily activities, and more recently to an emphasis on positive themes of happiness, social and emotional well-being, and quality of life,” as well as equity and justice in the distribution of health care across societies (Labonte 2000; McDowell and Newell 1996; Morreim 2000; Riley 1987). For the individual, healthiness changes over the life course and involves not only an internal assessment of health and well-being against one’s own prior health and personal expectations, but also an external view of one’s health in reference to others and to societal expectations.

Recent debate over the concept of health in the United States has also resulted from health care reform and associated efforts to define coverage and medical necessity or to identify the purpose of health care (Morreim 2000). The debate involves both ethical and philosophical issues and cannot be separated from the pressures of technology or the varying political and economic perspectives of many stakeholders, including, of course, the profession of medicine itself. Labonte (2000), writing for the Hastings Center on the health promotion/disease prevention movement, compares three health “explanatory systems”—medical, behavioral, and socio-environmental—in terms of the compatibility of each with either a libertarian or social justice theory of the common good. This perspective is directly relevant to disputes within the profession of medicine over where responsibility for health lies. Engel recognized this tension 25 years ago in his description of a Rockefeller Foundation seminar on the concept of health, where participants argued that only the organic elements of disease constituted “real” disease and that “the physician should not be saddled with problems that have arisen from the abdication of the theologian and the philosopher” (Engel 1977).

THE INTERACTIVE BIOPSYCHOSOCIAL MODEL (IBM)

The IBM is based on the IOM concept of health and the following core principles: (1) an orientation toward health rather than illness; (2) analytic capacity for outcomes of health or illness; (3) parity among the three domains of capital (biophysical, psychocognitive, and social) as factors in an individual’s health endowment; (4) bi-directional causality and feedback (i.e., biopsychosocial capital influences the health endowment and the endowment influences access to and use of biopsychosocial resources); (5) primacy of the multi-actor frame (i.e., analysis of

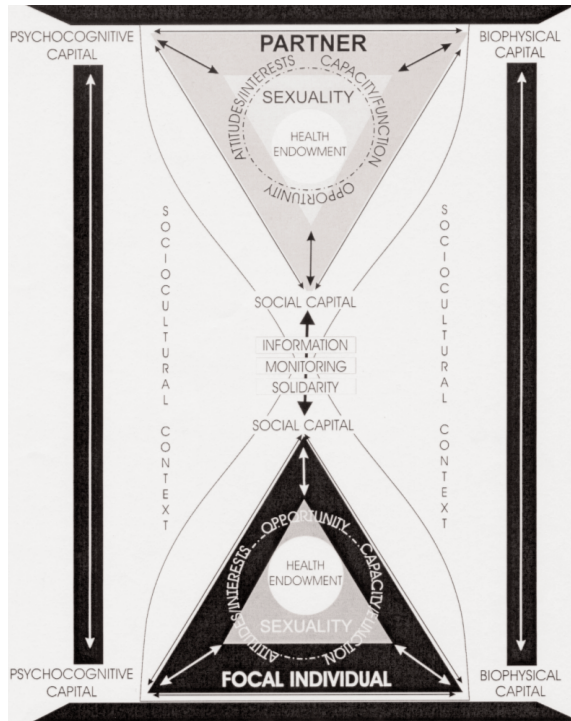


FIGURE 1

The Interactive Biopsychosocial Model (IBM).

individual health or illness embedded in the partner, the family, or other explicitly defined social networks); (6) interdependency of social and life course dynamics; and (7) the potential of capital inputs to act as assets or liabilities. (See Figure 1.)

Creating and using a dynamic, health-centered model requires an explicit vocabulary to describe and explain the relationships between its core components: the biophysical, psychocognitive, and social dimensions of health. We propose a vocabulary that draws on the socioeconomic concept of *capital* to specify biophysical, psychocognitive, and social inputs to health. This vocabulary makes it possible to view the components of health as potential assets or liabilities and reinforces the dynamic function of the model, because stocks of capital change over time (O’Rand 2001).

The application of economic principles to the construction of health models is not new (see, for example, Becker 1964; Cutler and Richardson 1998; Grossman 1972). Grossman proposes that “good health” be viewed as a durable capital stock inherited by individuals. The stock increases with investment and depreciates with age; other factors—such as education, gender, or ethnicity (“human capital”)—may positively or negatively affect the rate of health depreciation and efficiency in acquiring good health over time.

Biophysical, psychocognitive, and social capital comprise an individual's *health endowment*. Biophysical capital includes genetic composition, physiology, physique, sensory function, nourishment, strength, and appearance. Investments in biophysical capital affect an individual's physical and physiological capacity for health. Psychocognitive capital includes intelligence, emotions, well-being, personality attributes, self-esteem and self-efficacy, coping, and resilience. Investments of this type determine attitudes, interests, and desires related to health. Social capital refers to the networks of dynamic relationships with others (kin, friends, neighbors, physicians) who encourage or sanction certain kinds of behavior, and the social connectedness and social constraints that result. Investment in social capital through monitoring, provision and sharing of information, and solidarity (companionship, love, advocacy) with another determines how much access an individual has to the health endowment (Sandefur and Laumann 1998). We distinguish "social capital" from the notion of "sociocultural context," a frequently invoked but vague term. In this model, "sociocultural context" is defined as the broader environment of social locations (ethnic, religious, gender, political, or economic class) and summarizes the set of social expectations and norms as well as socially determined conditions, such as differential access to scarce resources, that influence individuals' health.

The health endowment of the individual is inextricably linked to socially relevant others (partner, kin, friend). This mutual dependency for health involves pooling resources, sharing capital, and negotiating joint resources. In our model, this interdependency allows two healthy individuals acting jointly to generate a surplus greater than each would generate alone. The interdependency occurs through repeated small exchanges and specialization of roles within the relationship, and serves to maximize efficiency and efficacy and to perpetuate the interdependency. If individuals have disparate levels of health (one with a large health endowment, the other with a small endowment) or are both in bad health, they may generate a net surplus or a deficit, depending on their relative health, the trajectory of health prior to and within the relationship, and the sociocultural context.

In our model, the health endowment can grow and contract over time, but at any given time, it is finite and quantifiable. Expansion of an individual's health endowment might occur when an individual begins an intimate partnership. Contraction of the endowment could occur by acquisition of a disease. Individuals may also shift capital resources from one area to another, to stabilize the health endowment and to compensate for specific health challenges. Because the endowment is finite at any given time, investment in biophysical capital, for example through exercise (often a solo activity such as running or biking), could draw resources away from psychocognitive or social capital, although the exchange need not be one-to-one. Alternatively, where physical capital is lowered, social capital may be used to compensate (e.g., a woman with a hip fracture calls

on her partner to assist her with dressing and bathing). Alzheimer's disease may erode psychocognitive capital, but reallocating time or energy to physical capital or social support may lessen the impact of dementia on overall health. Reallocation of resources to maximize health depends on an individual's connections to significant others and the constraints imposed by these connections. Partnerships characterized by mutually high social capital are the most efficient and show the greatest resilience to health threats. Sociocultural context heavily influences the value and meaning of different kinds of health capital to the individual and affects the extent to which one kind of capital can be substituted for another.

Consistent with systems theory, the life course developmental perspective views adult development as an ongoing process in which continuity and change interact in complex ways (Baltes 1987; Elder 1992; O'Rand and Krecker 1990). Transitions and continuity in the life course constitute adult development and well-being, and the impact of changes and the negotiation of conflicts depend on the social context in which they occur (Bengston and Allen 1993; Riley, Foner, and Waring 1988). We use the life course perspective with a focus on dyadic intimate partnerships to understand mature adult sexuality as adult human development unfolds.

In Figure 1, the lower triangle represents the focal individual who connects to a partner represented by the upper triangle. In this case (a study of sexuality and health), an intimate partner is the "other," but the framework allows for the other to be defined by any primary social connection of interest (the family, a religious congregation, a physician, etc.). This social bond occurs through and within a network of social connections that confer three key bi-directional benefits and constraints: information, monitoring through influence and control, and social solidarity (Sandefur and Laumann 1998). An individual's social ties may facilitate acquisition of or limit access to pertinent health information. Social ties also exert positive or negative constraints on the individual's health activities and promote or detract from a person's sense of social support (Youm and Laumann 2002). The triangles link the three forms of capital that comprise the health endowment, and the hourglass shape symbolizes the importance of time in the life course perspective.

A central challenge presented by the theoretical framework presented here is the articulation and application of a common metric for quantifying varying types of capital. In application of the model to research questions involving populations, this can be overcome using relative positioning and rank-ordering of individuals along scales of each component type of capital. This approach has been proposed by Oakes and Rossi (2003) in the measurement of socioeconomic status in health research.

**APPLICATION OF THE IBM USING THE STUDY OF
SEXUALITY AND HEALTH AT OLDER AGES**

We define *sexuality* as physical capacity, opportunity for partnership and sexual conduct, and attitude. “Sexual capacity” includes the physiologic mechanisms of the sexual response cycle and relaxation, restoration, or physical release from sexual activity. “Sexual conduct” incorporates the activities undertaken to find and maintain a sexual partner. “Sexual attitude” refers to subjective states of desire or interest, beliefs, willingness, preferences, and satisfaction. Capacity, opportunity, and attitude comprise individual-level attributes of sexuality. *Intimacy*, by contrast, refers to the quality of the dyadic relationship; it describes a quality or condition involving close personal familiarity and feelings of warmth, closeness, and common or shared fate.

A strict biomedical hypothesis relating sexuality to health would propose that illness, disability, or reliance on medication(s) predict compromised sexual function. The medical model would say that good health predicts intact sexual function at older ages; that is, people who maintain or improve their health will maintain or improve their sexual function. Likewise, people who become ill, disabled, or dependent on medication, or who experience progressive illness will experience deterioration of sexual function. The emphasis here is on the physical and physiological aspects of disease and sexuality and on the individual.

Using the interactive biopsychosocial perspective, however, we posit an interaction between an individual’s own health and the partner’s health as crucial to sexuality, health, and illness. Further, we hypothesize that the expression of sexuality at older ages enhances the beneficial effects and minimizes the detrimental effects of aging on the health of both individuals in the relationship, and also acts as a buffer against chronic illness, physical disability, medication use, cognitive decline, depression, and social isolation at older ages. In socioeconomic terms, sexuality mediates the allocation of resources to the three domains of capital comprising the health endowment. Because health is constructed in relation to another person, the distribution of one individual’s resources for the maintenance of health, which may slow the depreciation of health with age, has a direct impact on the other person’s capital resources and the couple’s joint endowment of health.

The relationship between sexuality and health is bi-directional. We further hypothesize that older adults with chronic illness will experience greater compromise of sexual capacity, desire, and opportunity than otherwise similarly healthy counterparts. We expect that older adults whose partners are chronically ill will experience greater sexual dysfunction than others, and that this deficit will negatively affect their overall health.

Application of the IBM: The Case of Diabetes Mellitus

To illustrate the application of the IBM to a hypothesis about the relationship between older adult sexuality and the expression of chronic disease, we next explore the relationship between sexuality and type 2 diabetes mellitus.

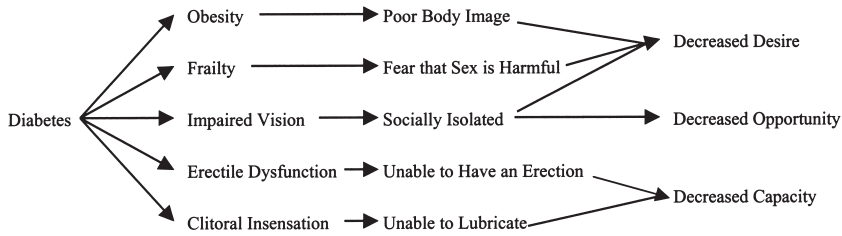


FIGURE 2

Effects of diabetes on sexual health.

Previous research on sexuality in diabetics has focused on the relationship between neurovascular changes and physical sexual function problems such as erectile dysfunction in men (Bokhour et al. 2001; Korenman 1998; Rosen 1996). Despite a major international attempt to understand the relationship between sexuality and diabetes in women (Nicolosi et al. 2002), empirical evidence about the physiologic, psychologic, and social mechanisms is lacking. A strict biomedical hypothesis relating sexuality to diabetes would propose that diabetes predicts compromised sexual function (in particular, erectile dysfunction) at older ages. Over time, age itself will affect sexuality, primarily through physiologic mechanisms. The process and experience of aging may impair sexual function (e.g., vaginal dryness due to estrogen loss in women, or prolonged time to erection in men) or enhance it (more leisure time, equalization of need for foreplay, or deeper awareness of partner's desires and needs). We hypothesize that people with diabetes who maintain or improve their health will maintain or improve their sexual function. The model also predicts that people with poor glycemic control, disabling disease, or insulin dependence will experience deterioration of sexual function.

The IBM allows for an expanded set of hypotheses that incorporate a broader range of physical impairments affecting sexual function among diabetics, such as obesity, frailty, or visual impairments. We can also take into account the *partner's* obesity, frailty, or visual impairments as a determinant of the sexual health of individuals with diabetic partners. (See Figure 2.)

Using the IBM, we hypothesize that diabetics with intact sexuality and strong intimate relationships (intact capacity, interest, and opportunity) exhibit better physical and psychocognitive health, glycemic control, and social functioning at older ages than do similar diabetics with compromised sexuality. We also hypothesize that those with diabetic partners with compromised sexuality will show poorer physical and psychocognitive health and social functioning than those with either healthy partners or with diabetic partners with intact sexuality.

Further, if we consider the relationship between sexuality and chronic illness to be bi-directional, we hypothesize that, over time, sexual health protects against or slows the development of Type II diabetes and associated illnesses at older ages by enhancing the beneficial effects and minimizing the detrimental effects of

aging on health. In one direction, preservation of sexuality and intimacy lessens the burden of diabetes (e.g., physical activity, feeling of well-being, control, hopefulness, prolongation of independence) and provides biopsychosocial resources for a better quality of life. In the other direction, diabetes diminishes the benefits (e.g., more time for enjoying relationships, less inhibition, more physical attunement to partner's needs) and complicates the detrimental effects (e.g., less intense orgasms, heightened self-consciousness about body image, tougher competition for partners) of aging on sexuality. These hypotheses are supported by pilot work on this subject and form the basis for a national longitudinal study to examine the role of sexuality in mitigating or ameliorating the impact of illness on health at older ages.

CONCLUSION

The 20th century has witnessed astonishing accomplishments in modern medicine. Prevailing models of illness and disease, in combination with technological advances, have transformed our ability to detect and treat disease, and have eradicated many life-shortening illnesses. These successes have significantly extended the human life span and have enhanced the quality of life in industrialized nations. Yet, this unprecedented demographic shift toward longer, healthier life presents an important opportunity to build on traditional, biomedical models of health. The IBM is not meant to detract from the strengths of purely biomedical models, but rather to build on those models and include social and psychological factors affecting diverse biological systems. A strength of the IBM is the explicit incorporation of partners and larger social networks, as well as the social and cultural context in which the individual is embedded. The IBM adds to the repertoire of researchers and practitioners in medicine and health sciences, and gives them a dynamic framework for building scientific or clinical hypotheses about the etiologies and consequences of health, well-being, and disease throughout the life course.

The IBM can be applied to a wide range of questions about health outcomes and the processes that produce them, including, for example, adaptation to and course of disease for those with cancer, heart disease, hearing loss, dementia, or other diseases; the effects of disease in spouse, child, or social other on self; the impact of group beliefs, attitudes, and practices on development of disease and maintenance of health. The model also could be used to address health issues in public policy that include developing individual and group interventions to improve health practices, and establishing a public infrastructure that expects, facilitates, and promotes scientific collaboration between disciplines and institutions, both national and international.

A model for health that expands beyond the biomedical model is not meant to relegate all responsibility to the medical profession. On the contrary, the ideals of interdisciplinary collaboration in research, education, and the provision of

health care is a fundamental inspiration of this model and will determine its success. New opportunities and new challenges require an integrated, interdisciplinary approach, drawing on the impressive advances in biology, medicine, psychology, sociology, economics, and many other disciplines. We will move forward fastest and most efficiently if we link arms, model jointly, and build together.

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APPENDIX B, Part 1

Rating Scale

(Source: Christopher Clark)

PARTICIPANTS'S NAME: _____ DATE: _____

PERSON COMPLETING FORM: _____

Please circle the most appropriate answer.

Do you live with the participant? No Yes

How much contact do you have with the participant?

- Less than 1 day per week 3-4 days/week
 1 day/week 5 or more days per week
 2 days/week

Relationship to participant

- Self Spouse Sibling Child Other Family Friend Other _____

In each section, please circle the number that most closely applies to the participant. This is a general form, so no one description may be exactly right -- please circle the answer that seems to apply most of the time.

Please circle only one number per section, and be sure to answer all questions.

MEMORY

- 0 Normal memory.
- 1 Occasionally forgets things that they were told recently. Does not cause many problems.
- 2 Mild consistent forgetfulness. Remembers recent events but often forgets parts.
- 3 Moderate memory loss. Worse for recent events. May not remember something you just told them. Causes problems with everyday activities.
- 4 Substantial memory loss. Quickly forgets recent or newly-learned things. Can only remember things that they have known for a long time.
- 5 Does not remember basic facts like the day of the week, when last meal was eaten or what the next meal will be.
- 6 Does not remember even the most basic things.

SPEECH AND LANGUAGE

- 0 Normal ability to talk and to understand others.
- 1 Sometimes cannot find a word, but able to carry on conversations.
- 2 Often forgets words. May use the wrong word in its place. Some trouble expressing thoughts and giving answers.
- 3 Usually answers questions using sentences but rarely starts a conversation.

- 4 Answers questions, but responses are often hard to understand or don't make sense. Usually able to follow simple instructions.
- 5 Speech often does not make sense. Can not answer questions or follow instructions.
- 6 Does not respond most of the time.

RECOGNITION OF FAMILY MEMBERS

- 0 Normal - recognizes people and generally knows who they are.
- 1 Usually recognizes grandchildren, cousins or relatives who are **not** seen frequently but may not recall how they are related.
- 2 Usually does not recognize family members who are not seen frequently. Is often confused about how family members such as grandchildren, nieces, or nephews are related to them.
- 3 Sometimes does not recognize close family members or others who they see frequently. May not recognize their children, brothers, or sisters who are not seen on a regular basis.
- 4 Frequently does not recognize spouse or caregiver.
- 5 No recognition or awareness of the presence of others.

ORIENTATION TO TIME

- 0 Normal awareness of time of day and day of week.
- 1 Some confusion about what time it is or what day of the week, but not severe enough to interfere with everyday activities.
- 2 Frequently confused about time of day.
- 3 Almost always confused about the time of day.
- 4 Seems completely unaware of time.

ORIENTATION TO PLACE

- 0 Normal awareness of where they are even in new places.
- 1 Sometimes disoriented in new places.
- 2 Frequently disoriented in new places.
- 3 Usually disoriented, even in familiar places. May forget that they are already at home.
- 4 Almost always confused about place.

ABILITY TO MAKE DECISIONS

- 0 Normal - as able to make decisions as before.
- 1 Only some difficulty making decisions that arise in day-to-day life.
- 2 Moderate difficulty. Gets confused when things get complicated or plans change.
- 3 Rarely makes any important decisions. Gets confused easily.
- 4 Not able to understand what is happening most of the time.

SOCIAL AND COMMUNITY ACTIVITY

- 0 Normal - acts the same with people as before
- 1 Only mild problems that are not really important, but clearly acts differently from previous years.
- 2 Can still take part in community activities without help. May appear normal to people who don't know them.
- 3 Often has trouble dealing with people outside the home without help from caregiver. Usually can participate in quiet home activities with friends. The problem is clear to anyone who sees them.
- 4 No longer takes part in any real way in activities at home involving other people. Can only deal with the primary caregiver.

- 5 Little or no response even to primary caregiver.

HOME ACTIVITIES AND RESPONSIBILITIES

- 0 Normal. No decline in ability to do things around the house.
- 1 Some problems with home activities. May have more trouble with money management (paying bills) and fixing things. Can still go to a store, cook or clean. Still watches TV or reads a newspaper with interest and understanding.
- 2 Makes mistakes with easy tasks like going to a store, cooking or cleaning. Losing interest in the newspaper, TV or radio. Often can't follow a long conversation on a single topic.
- 3 Not able to shop, cook or clean without a lot of help. Does not understand the newspaper or the TV. Cannot follow a conversation.
- 4 No longer does any home-based activities.

PERSONAL CARE - CLEANLINESS

- 0 Normal. Takes care of self as well as they used to.
- 1 Sometimes forgets to wash, shave, comb hair, or may dress in wrong type of clothes. Not as neat as they used to be.
- 2 Requires help with dressing, washing and personal grooming.
- 3 Totally dependent on help for personal care.

EATING

- 0 Normal, does not need help in eating food that is served to them.
- 1 May need help cutting food or have trouble with some foods, but basically able to eat by themselves.
- 2 Generally able to feed themselves but may require some help. May lose interest during the meal.
- 3 Needs to be fed. May have trouble swallowing.

CONTROL OF URINATION AND BOWELS

- 0 Normal - does not have problems controlling urination or bowels except for physical problems.
- 1 Rarely fails to control urination (generally less than one accident per month).
- 2 Occasional failure to control urination (about once a week or less).
- 3 Frequently fails to control urination (more than once a week).
- 4 Generally fails to control urination and frequently can not control bowels.

ABILITY TO GET FROM PLACE TO PLACE

- 0 Normal, able to get around on their own. (May have physical problems that require a cane or walker).
- 1 Sometimes gets confused when driving or taking public transportation, especially in new places. Able to walk places alone.
- 2 Cannot drive or take public transportation alone, even in familiar places. Can walk alone outside for short distances. Might get lost if walking too far from home.
- 3 Cannot be left outside alone. Can get around the house without getting lost or confused.
- 4 Gets confused and needs help finding their way around the house.
- 5 Almost always in a bed or chair. May be able to walk a few steps with help, but lacks sense of direction.
- 6 Always in bed. Unable to sit or stand.

APPENDIX B, Part 2

Instructions for Applying Seven-Minute Screen

(Source: Christopher Clark)

Supplies Needed:

- Pencil
- Blank sheet of paper
- Stopwatch

First you introduce yourself to the patient and shake their hand. Then request that they be seated as comfortable as possible. Then start the dialogue.

Say to patient:

I would like to ask you some questions to check your memory and concentration. Some of them may be easy and some of them may be difficult.

Lets start:

Date:

What is the day of the week?
What is today's date?
What month are we in?
What is the year?

Address:

Can you please tell me what is your home address?
What city?
What is your zip code?

Phone Number:

Can you please tell me your home phone number starting with the area code?

Memory:

Ask the subject to repeat and remember/memorize three words.
Please read the words at one second per word (intervals). .

Serial Subtraction:

Say to patient: We are going to do a math exercise. Lets start with a 100 and we take away three (3) and we are left with 97. Now please take away/subtract three (3) from 97. Now taking away/subtract three (3) from every new number until I say stop.

Clock Draw:

Place a blank sheet of paper and pencil with eraser. Say to the subject: Draw the face of a clock. Put in all the numbers and than set the hands to eight-twenty or twenty after eight.

Verbal Fluency:

Say to patient: Tell me as many animals as you can think of as fast as you can until I tell you to stop.

(Make sure that you write down the animals that are given. This way you can track if the patient has repeated any animals.)

Delay recall:

Say to patient: A few minutes ago I said three words. What were the three words that I asked you to remember? Or “Do you remember the three words that I asked you to remember a few minutes ago?” Can you tell me what they were?

Scoring of Seven-Minute Screen

Correct =0

Errors =1

Date:

The exact date, day of week, month and year must be given.

Address:

Home address or location address is acceptable

Phone:

Recent area code and number must be given. If patient gives an old number or someone else's number its not acceptable.

Memory:

All three words must be repeated back to the examiner: Up to three tries.

Serial Subtractions:

If patient has an education level lower than 12 yrs, still do, but if patient gets it wrong do not consider for scoring purpose. If patient gets it correct, please give credit. This test is based on educational level.

Clock Draw:

Allow patient to erase if they make a mistake. If patient forgets the time that you indicated, please repeat full instructions (not partial instructions). For scoring please see sample sheet of clocks.

Verbal Fluency:

Make sure that the examiner writes down all the animals that the patient has said. The reason for this is that we want to track any perseverative responses. Perseverative responses are when the same word is being repeated.

Delay recall:

If the patient gives you any other word other than the three original words, please write them down. We can track for any intrusions. Intrusions are words that are not on the original list of words.

APPENDIX B, Part 3

Cognitive & Functional Screen

Patient Information

(Source: Christopher Clark)

Name: _____
Address: _____
Telephone: _____

DOB: _____

Education: _____

Gender: Male Female

Race: White Black American Indian Pacific Island Multi-racial

Ethnicity: Hispanic Non-Hispanic

Informant Information

Name: _____
Address: _____
Telephone: _____

Relationship to patient: Spouse Child Other family Other: _____

Medical Problems: _____ Any Cognitive Complaints? Yes No
_____ If yes, please describe: _____

Action Taken:
 Refer for Diagnostic Evaluation
 Other: _____

Cognitive Results: _____

0-4 = normal
5-8 = mild cognitive impairment
> 8 = probable dementia
0-4 = normal
5-8 = mild cognitive impairment
8 = probable dementia

Functional Results: _____

ORIENTATION

IMPAIRMENT SCORE

Date:

Day of the week: _____

Day of the month: _____

Month: _____

Year: _____

Address:

Street & number: _____

Town/City: _____

ZIP: _____

Phone:

Area code: _____

Seven-digit number: _____

Memory:

Ask Subject: To repeat and remember three words (ball, flag, tree)

Serial Subtractions (**appropriate if education** \geq 12 years)

Give first example (100-3 = 97) Reset to correct # if subject errors

Score one point for each incorrect number (max = 4)

100- 97 -94 -91 -88 -85

Clock Draw

"Draw the face of a clock. Put in all the numbers, and set the hands to eight-twenty or twenty after eight."

0 = normal

1 = mildly impaired

2 = moderately impaired

3 = severely impaired

Verbal Fluency

Number of unique animals in 60 seconds: _____

0 = > 12 animals

1 = 9-12 animals

2 = 5-8 animals

3 = < 5 animals

Delayed Recall

(Score number of words not recalled)

Ball - Flag - Tree

Total Errors:

Functional Assessment

PARTICIPANTS'S NAME: _____ DATE: _____

PERSON COMPLETING FORM: _____

RELATIONSHIP TO PATIENT: _____

In each section, please circle the **one number** that **most closely applies** to the patient. This is a general form, so no one category may be exactly right -- please circle the answer that seems closest at this time.

Please circle only one number per section.

MEMORY

- 0 Normal memory.
- 1 Occasionally forgets things that they were told recently. Does not cause many problems.
- 2 Mild consistent forgetfulness. Remembers recent events but often forget parts.
- 3 Moderate memory loss. Worse for recent events. May not remember something you just told them. Causes problems with everyday activities.
- 4 Substantial memory loss. Quickly forgets recent or newly learned things. Can only remember things that they have known for a long time.

LANGUAGE

- 0 Normal ability to talk and understand others.
- 1 Sometimes cannot find a word, but able to carry on conversations.
- 2 Often forgets words. May use the wrong word in its place. Some trouble expressing thoughts and giving answers.
- 3 Usually answers questions using sentences but rarely starts a conversation

DATE AND TIME

- 0 Normal awareness of the time and which day of the week it is.
- 1 Some confusion about what time it is or what day of the week it is, but the problem is not severe enough to interfere with everyday activities.
- 2 Frequently confused about the date and/or time.

ABILITY TO MAKE DECISIONS

- 0 Normal - as able to make decisions as before.
- 1 Only some difficulty making decisions that arise in day-to-day life.
- 2 Moderate difficulty. Gets confused when things get complicated or plans change.

ABILITY TO GET FROM PLACE TO PLACE

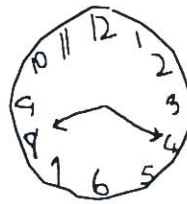
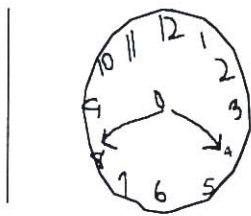
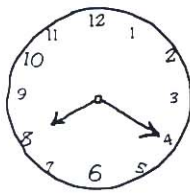
- 0 Normal. Able to get around on their own. (May have physical problems that require a cane or walker).
- 1 Sometimes gets confused when driving or taking public transportation, especially in new places. Able to walk places alone.
- 2 Cannot drive or take public transportation alone, even in familiar places. Can walk alone outside for short distances. Might get lost if walking too far from home.

APPENDIX B, Part 4

Clock Scoring

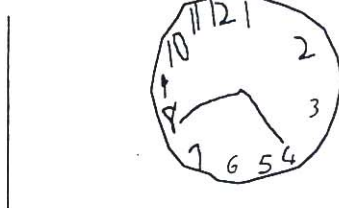
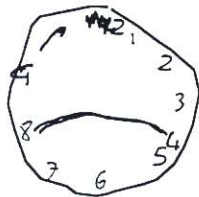
(Source: Christopher Clark)

NORMAL



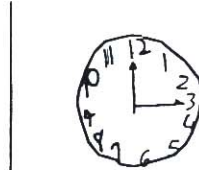
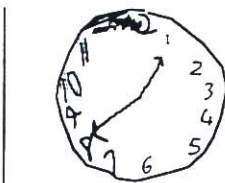
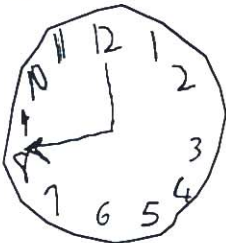
Score = 0

MILD IMPAIRMENT



Score = 1

MODERATE IMPAIRMENT

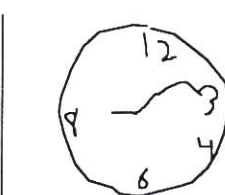


Score = 2

SEVERE IMPAIRMENT



8:20



Score = 3