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Alzheimer's Disease Clinical Research

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Outline

- What do we know about Alzheimer's Disease and its treatment?
- What types of Alzheimer's Disease research are needed?
- Why are Alzheimer's Disease patients needed in clinical research?

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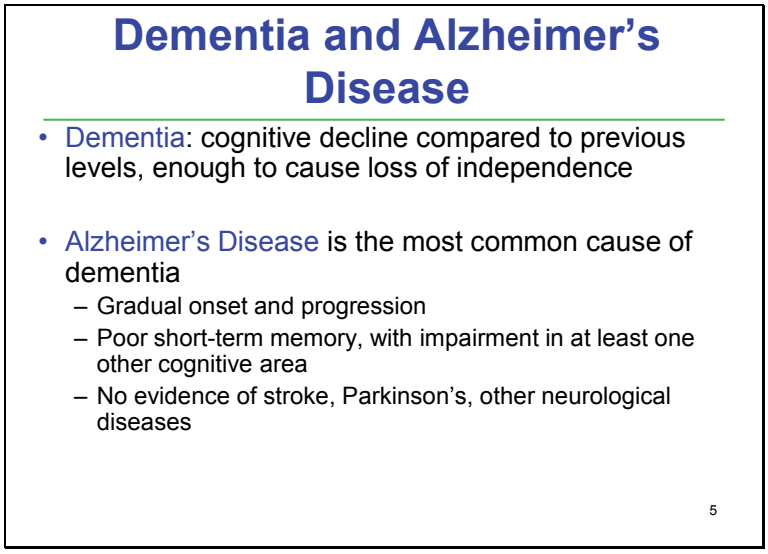
What Do We Know about Alzheimer's Disease and its Treatment?

Slide 5



Dementia can be caused by multiple diseases. Alzheimer's disease is the most common disease that causes dementia. There are other diseases that we won't talk about here that also cause dementia such as cerebrovascular disease (vascular dementia) and Lewy Body disease (associated with Parkinson's disease) as well as the frontotemporal dementias. Mild cognitive impairment is the term that describes the grey zone between normal mental function and early dementia.

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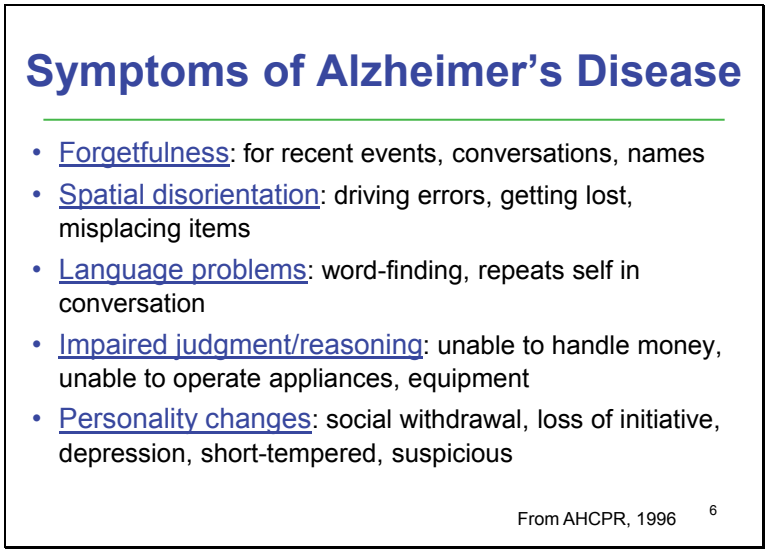

Memory loss - actually a difficulty with learning new things - is usually the principal symptom in Alzheimer's. The symptoms in the other cognitive domains may be equally challenging to deal with, but they are more variable from person to person with Alzheimer's.

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How Alzheimer's Disease is Diagnosed

- A patient is brought to a physician, usually by a family member.
- Ideally, a physician would do:
  - Thorough medical history
  - Obtain details of duration and nature of cognitive difficulties
  - Perform mental status exam and neurological exam
  - Review CT or MR of brain
  - Check a few selected blood tests
  - Order detailed neuropsychological testing if circumstances require

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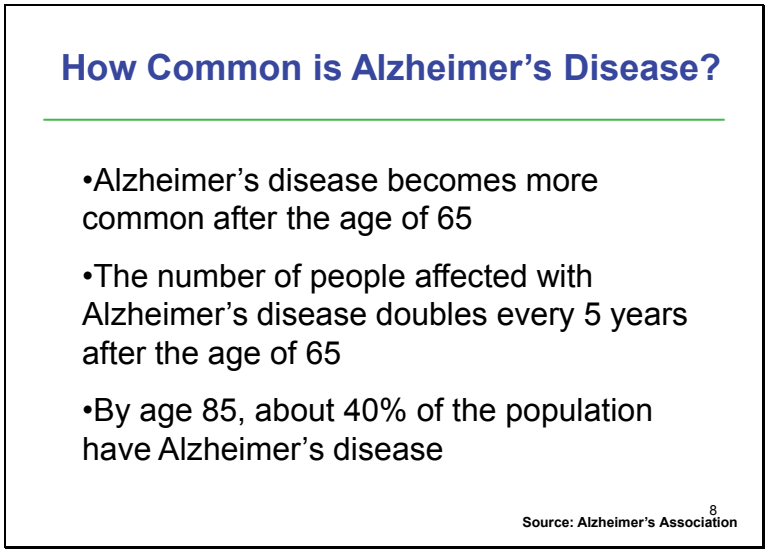

Alzheimer's is largely but not exclusively a disease of the elderly. It does occur in people under age 65, however.

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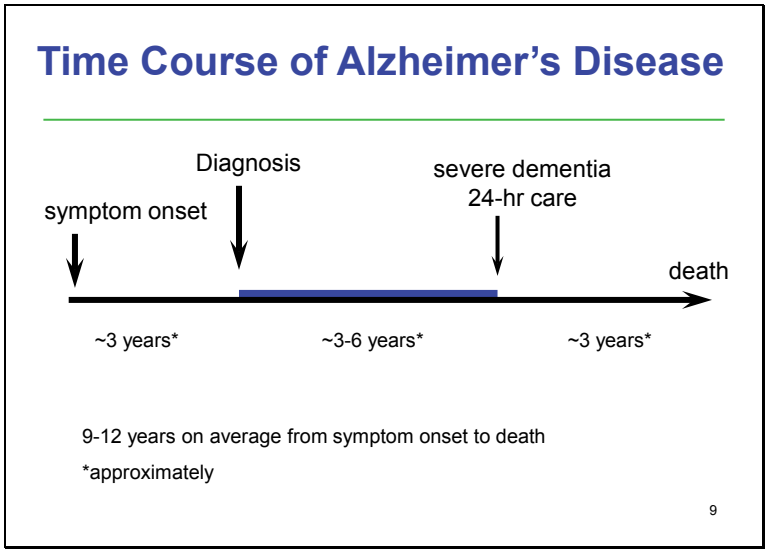

This slide shows the natural history of Alzheimer's. There is a considerable time period between the onset of symptoms and diagnosis. If we had a way of making very early diagnoses, we could theoretically begin to treat the disease earlier than we currently are able to. Now, treatment occurs during the symptomatic window. At the end of the disease, there can be a long time between when severe dementia is present and death occurs, hence the costliness of long term care. Survival in the severe stage of the disease can be several years.

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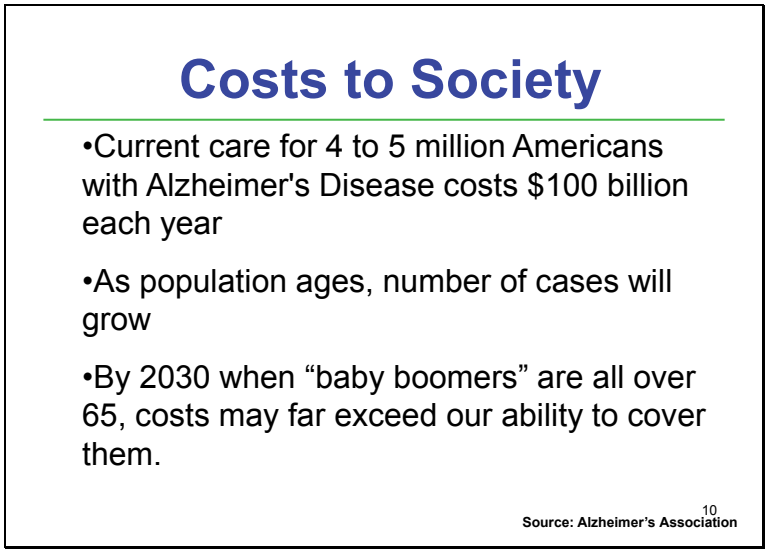

The biggest cost from Alzheimer’s is the cost of long term care. The average yearly costs are probably more than $40,000 per person for people with Alzheimer’s in nursing homes or assisted living facilities.

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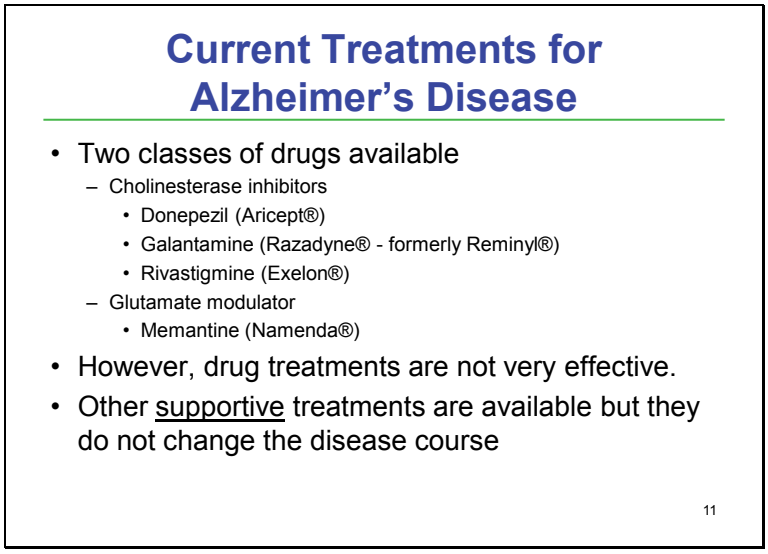

There have been 4 drugs approved for the treatment of Alzheimer's Disease since 1994. The most recently approved drug was memantine, whose trade name is Namenda.

Supportive treatment refers to education of caregivers, social services like home health aids, transportation services, day care, respite care, as well as things like financial planning.

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Effectiveness of Current Treatments

- The best outcome to be hoped for with current medications is the delay of worsening of symptoms.
  - Have very modest effects on average
  - The effects do not last very long
- Improvement is very rare.

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The key issue is that the currently available drugs have very modest benefits. Therefore, there is a pressing need to develop more effective treatments.

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What Types of Alzheimer's Disease Research Are Needed?

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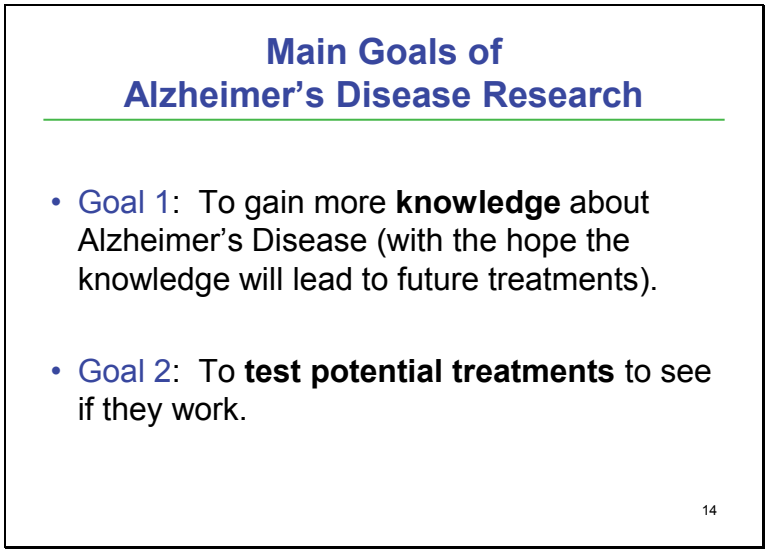

Of course, some research studies will have both goals.

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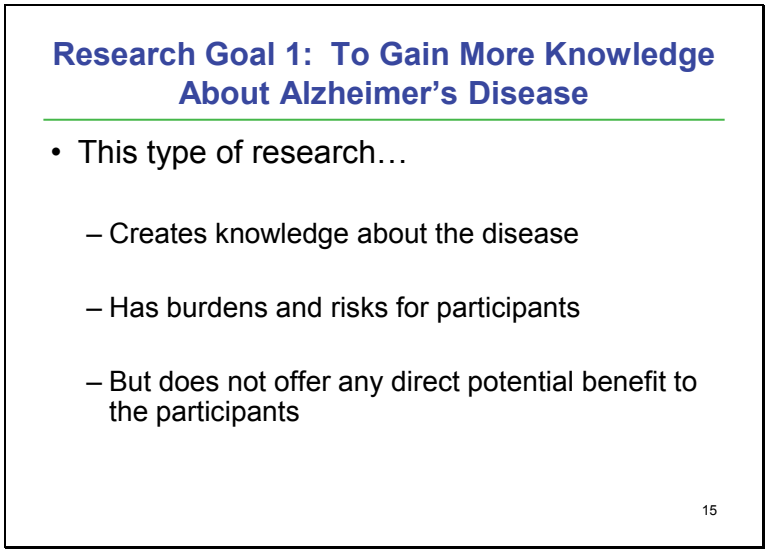

Drug trials are more than just taking a drug. There are various assessment procedures that are necessary to see if the drug is working, and also to see how it works. Researchers and regulators at the US FDA have become more interested in understanding how the drug affects the brain and the fluid that surrounds the brain (called spinal fluid). Thus, there is an increasing emphasis on doing brain scans and measuring things in the spinal fluid during the course of the taking of medications in a study.

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Research Goal 1: To Gain More Knowledge About Alzheimer's Disease (continued)

- This type of research is often included in larger studies that test treatments.
- Examples of procedures used for this type of research:
  - Brain scans
  - Lumbar punctures
  - Genetic testing

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One Detailed Example: Lumbar Punctures

- Overview
  - Used to study fluid surrounding brain in patients with Alzheimer's Disease
  - Long needle inserted through lower back into the spinal canal
  - Patients given numbing medicine, but may experience small amount of pain
- Benefits
  - Provide view of brain chemistry not obtainable any other way
  - No direct benefit to subject but may lead to better understanding of Alzheimer's Disease to help future patients

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Lumbar punctures are generally regarded as safe, and well tolerated, especially in middle aged and older individuals.

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Lumbar Punctures, continued

- Risks
  - About 5% of patients will get headaches that go away with Tylenol (or other pain reliever)
  - 1% will get a severe headache that requires inserting a needle into the back again
  - Virtually no chance of any serious neurological disability
- Discomforts
  - Pain during the procedure, though not much worse than blood drawing
- [Ultimately, a safe procedure with minor discomfort, and rare severe headache]

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Headaches are the only common complication. They often are just a day or two, but if they are persistent, they can be effectively treated.

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Other Examples of Research Procedures to Create Knowledge

- Brain scans
- Blood tests, including genetic testing
- Others

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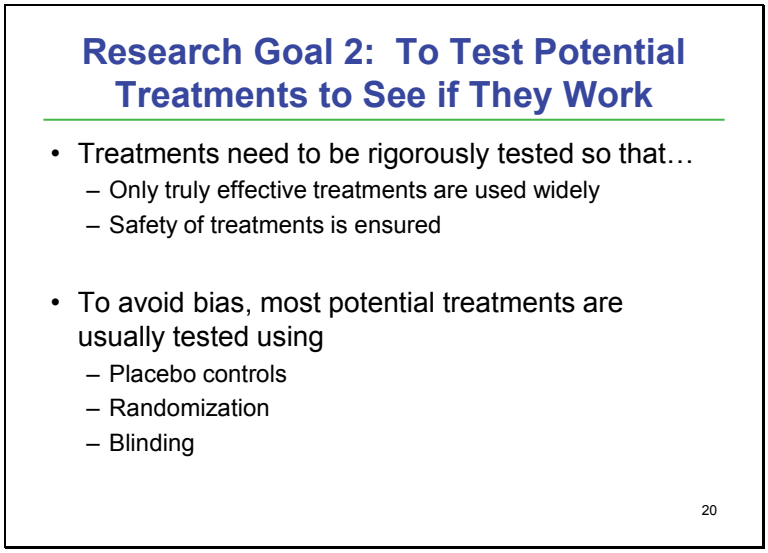

Placebo controls – Persons who enroll in a clinical trial are assigned to either the experimental intervention group or the control group. The control group receives inactive intervention or an inactive drug (placebo) in such a way that the subjects do not know what they are receiving. This is done to better see the effectiveness of the new drug or treatment and gives researchers a comparison group (those on the placebo).

Randomization – Whether a subject is assigned to the control group or the experimental treatment group is decided randomly. This process is like a coin toss that is done by computer. During clinical trials, no one likely knows which therapy is better, and randomization assures that treatment selection will be free of any preference a physician may have.

Blinding - ‘‘Blinding" helps ensure that bias doesn't distort the conduct of a trial or the interpretation of its results. A double-blind trial means that neither the participant nor the research team knows during the trial which participants receive the experimental treatment. Only the study pharmacist will know who receives which pill. The patient will usually find out what he or she received after the trial.

Research Goal 2: To Test Potential Treatments to See if They Work (cont.)

- This type of research involves…
  - Risks and burdens to participants.
  - Participants could possibly benefit, if the experimental treatment does work.
  - Essentially an experiment to see if a proposed treatment would work for people with Alzheimer's Disease in general.

Potential Treatment Studies

- We'll look at different types of research at different stages:
  - –New Drugs
  - –Vaccines
  - –Gene Transfer Therapy

Clinical Drug Development

- It takes 15 years on average for an experimental drug to progress from laboratory to clinics.
- Only 5 in 5,000 (0.1%) compounds that enter preclinical testing make it to human testing.
- Only 1 of those five is approved for sale.

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Clinical Phases of a New Drug

Laboratory Testing	Phase I	Phase II	Phase III	FDA Approval
Laboratory and animal studies conducted to show biological activity of the compound against the targeted disease. Compound is evaluated for safety.	Determine safe dosage & range. Identify side effects.	Determine effectiveness. Further evaluate safety.	Confirm drug's effectiveness. Monitor side effects. Compare it to commonly used treatments. Collect information that will allow the experimental drug or treatment to be used safely.	

•Some Phases may be combined

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Participation in a clinical trial requires a that the patient take on some risks with only a remote chance that the test drug will actually work as hoped. Yet, there is no way that progress will be made unless patients participate and accept some risks, ranging from no benefits to actual side effects.

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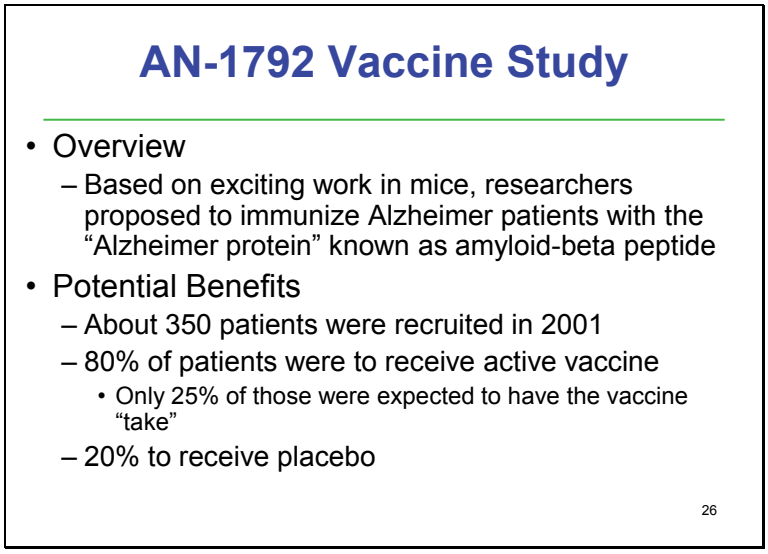

A study in mice genetically engineered to have something like Alzheimer's disease, published in 1999, showed dramatic reductions in the amount of Alzheimer brain pathology following a vaccination at middle age (for the mouse). Early but small safety studies in humans showed no serious safety concerns. Therefore a larger study was launched.

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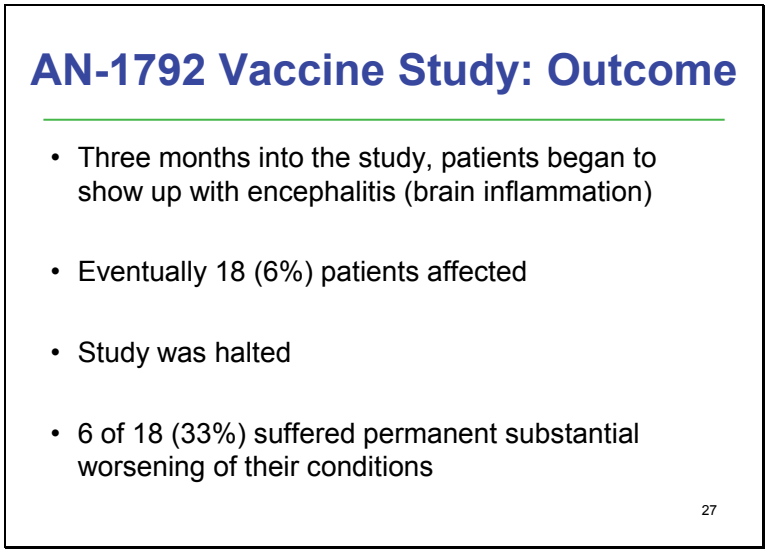

A sobering reminder of the risks. Some might say, "well it was only 18 people. This is a bad disease. The risk is worth it." But other people may not accept that logic, and may take the seriousness of the side effects as a criticism of the researchers for not predicting the risk in a smaller study. However, predicting side effects is a very difficult task.

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AN-1792 Vaccine Study

- Some analyses suggested therapy might have been beneficial
- Did risks to 6% justify halting trial?
- Was study begun prematurely, before sufficient safety data was available?

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The overall results from all eligible subjects did not show a substantial benefit of the vaccine. However, it appeared that there were some improvements on some of the more sophisticated memory measures. One troubling issue was that there was a significant change on the brain scans of people who were vaccinated, and that was that their brains got smaller! The significance of the brain scan findings is unknown.

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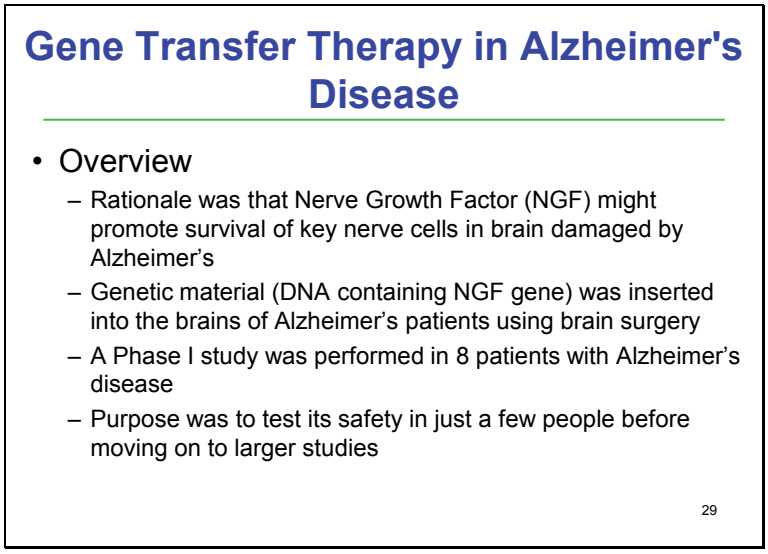

There was a theoretical basis for carrying out this trial. It was known from research studies in animals and humans that NGF promoted the growth of nerve cells known to be damaged in Alzheimer's disease. However, it was not clearly known whether this mechanism actually had anything to do with the cause of Alzheimer's or contributed in any material way to the progression of the disease.

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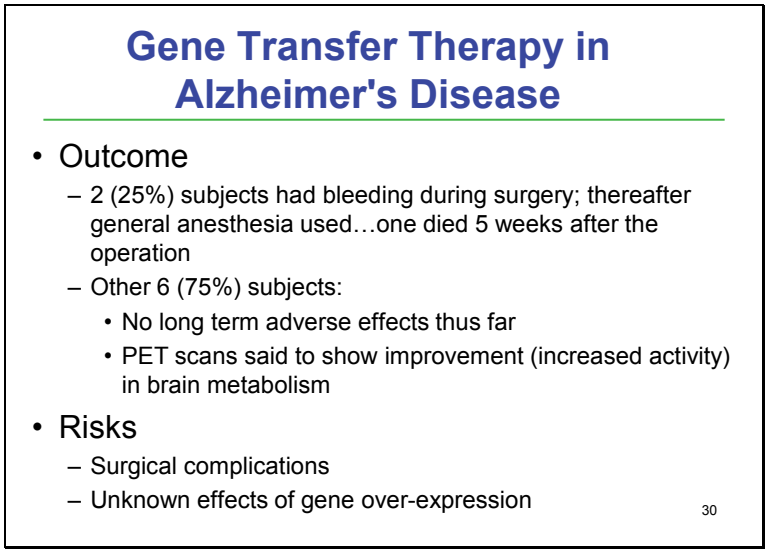

Phase I studies are critical to get some idea of safety of the therapy, but they cannot usually tell anything about whether therapy works. A trial with 6 subjects and no control group simply cannot tell us anything about whether the therapy worked.

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Why Are Alzheimer's Disease Patients Needed in Clinical Research?

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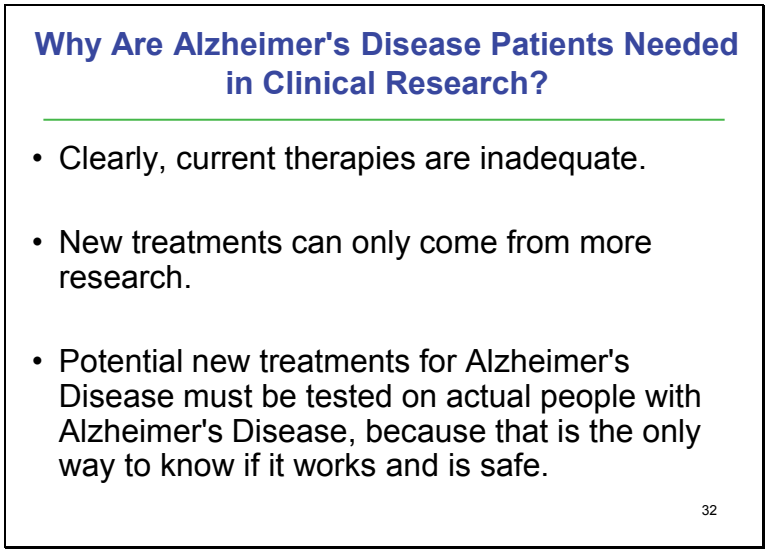

No matter how much testing is done on laboratory animals, Alzheimer's is fundamentally a human disease, and drugs need to be tested in humans to see if they work and to make sure they are safe for humans.

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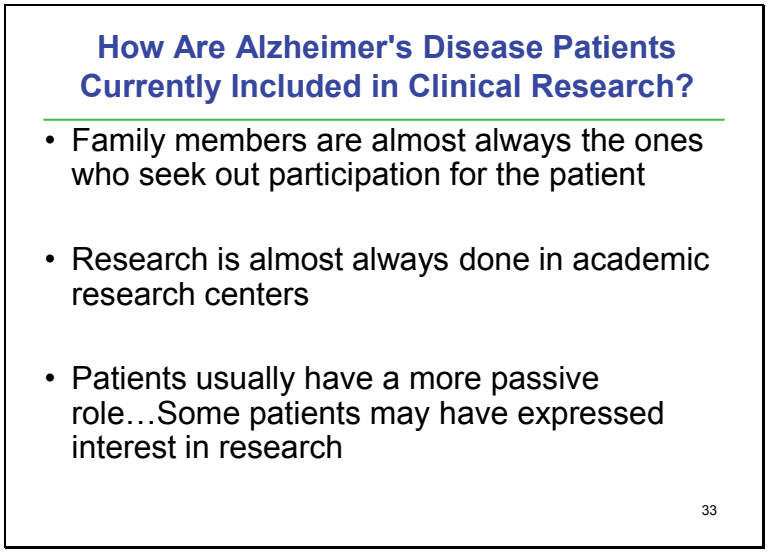

Participation in drug trials in Alzheimer's involves a partnership between the research team, the patient and a study partner (a fancy word that usually means either a spouse or an adult child). In my experience, it is very rare for a patient him or herself to initiate contact with physicians for Alzheimer's. Therefore it is the family who does so.

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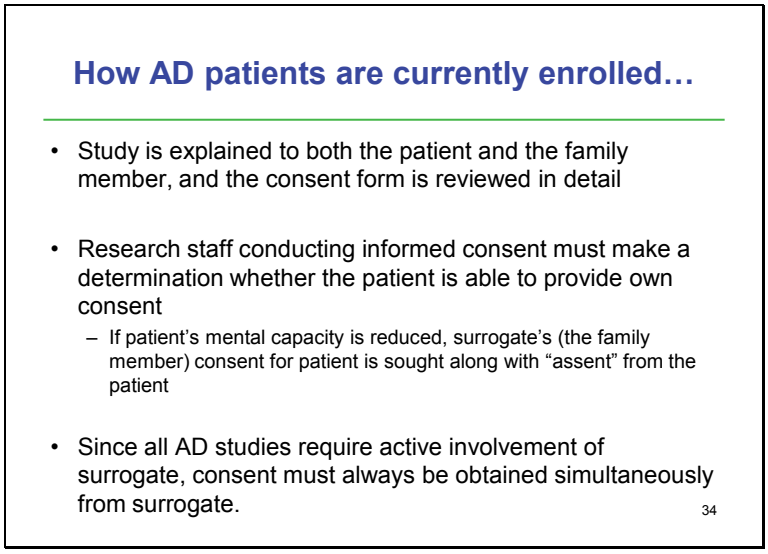

Initial contact could either be from surrogate, less likely patient, in response to an advertisement or announcement of a trial, or from study personnel reviewing records of persons previously seen at the research center who had expressed interest in future research.

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Current Alzheimer's Disease Research Participants Are…

- About 75 years old on average
- Mostly able to bathe and dress themselves
- Able to prepare simple meals and do simple chores
- Able to communicate conversationally in a way that might not appear abnormal to the casual observer
- In need of traveling with a companion
- But majority who participate, even if mild-to-moderate severity Alzheimer's Disease, cannot give their own informed consent

The Ethical Dilemma

- Alzheimer's is a common disorder that lacks an effective treatment
- Development of new therapies requires patient volunteers
- Participation in research involves a lot of time, some risks and possibly discomfort
- Alzheimer's Disease makes it impossible for most patients to give their own informed consent
- How should informed consent be obtained?

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Ethical Issues in Surrogate-Based Research

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Why Is Surrogate-Based Research Being Discussed?

- Much remains unknown about dementias
- For many studies, only people with dementia can be subjects
- Unless someone else (i.e., a surrogate) can give consent for them, this kind of research cannot take place
- But, what are the ethics of surrogate consent for research?

Outline

- How is clinical research currently regulated in the U.S.?
- How is surrogate-based clinical research currently regulated?
- Ethical questions that still need answers.

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How Is Clinical Research Currently Regulated in The United States?

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History of Research Ethics

- Until after World War II, little attention was paid to the ethics of research
  - Amount of research was small
  - Physician/researchers generally trusted not to harm their subjects
- Trial of Nazi doctors at Nuremberg began to call attention to need for focus on research ethics

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In order to better understand how we regulate research now, we need to understand the history of how the current system came about.

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Scandals Turn the Tide

- 1963 – Jewish Chronic Disease Hospital
  - Injection of cancer cells into elderly patients
- 1966 – Willowbrook State School
  - Injection of virus that causes hepatitis into mentally retarded children
- 1972 – Tuskegee
  - Long-term follow-up of African-American men with syphilis without providing treatment

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Jewish Chronic Disease Hospital case – Researchers looking to study the body's immunologic response to cancer injected cancer cells from other people into elder, debilitated or demented patients.
Willowbrook State School case – In a facility for children with mental retardation, where conditions were abysmal and almost all residents ultimately developed hepatitis (i.e., inflammation of the liver), researchers approached parents of children prior to admission to ask for consent to deliberately infect their children with hepatitis, to study the disease and its treatment. At times, the only unit at the facility with open beds was the research unit, meaning that the only way desperate parents could get their children admitted was to agree to the research study.
Tuskegee case – In 1932, the US Public Health Service began a long-term study of 200 black men with syphilis (i.e., an infectious, sexually transmitted disease) to observe the natural progression of the disease. Subjects were not told their diagnosis and were blocked from obtaining treatment, even when cheap effective treatment with penicillin became available in 1947. Many of the subjects died from syphilis, 40 wives were infected, and 19 children were born with congenital syphilis. The study was terminated when a physician/whistle-blower went to the press with the story.
These episodes and others led to progressively increasing pressure for closer oversight of medical research.

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Embodied in well-known statement of ethical principles, the Belmont Report, issued in 1979 by The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research.

Pharmaceutical companies conduct site visits to ensure compliance with research protocols.

Coordinating sites in multi-site research includes site visits and periodic retraining of research staff.

Data Safety Monitoring Boards (DSMBs) conduct periodic reviews of safety (e.g., side effects) and data to determine if the study should be modified or stopped.

The role of the FDA is explained on slide 48.
The role of the IRB is explained on slide 49.

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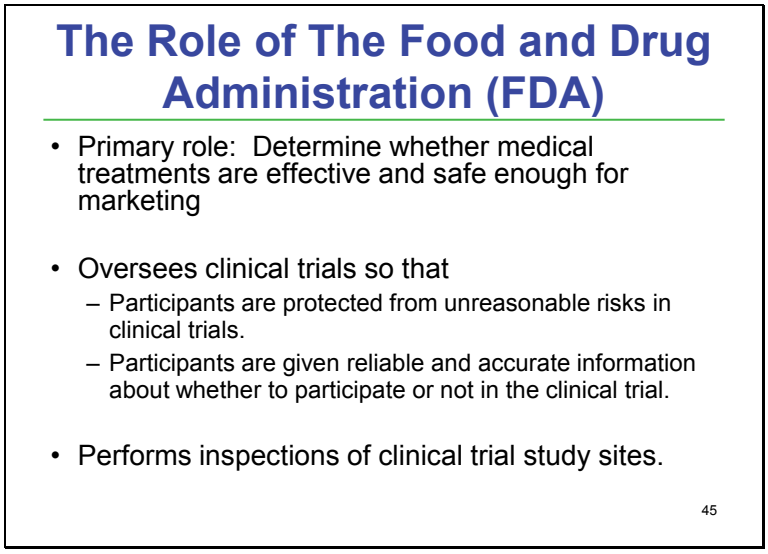

The Food and Drug Administration's job is to make sure medical treatments are safe and effective for people to use.
The FDA works to protect participants in clinical trials and to ensure that people have reliable information as they decide whether to join a clinical trial.
The federal government has regulations and guidelines for clinical research to protect participants from unreasonable risks.
The FDA does not develop new therapies, or conduct the clinical trials to demonstrate safety and effectiveness.
FDA staff members meet with researchers, and perform inspections of clinical trial study sites to protect the rights of participants and to verify the quality and integrity of the data.

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The 5 people must be of varying backgrounds, including at least one non-scientist and one person not affiliated with the institution.

Must have IRB approval before proceeding with research.

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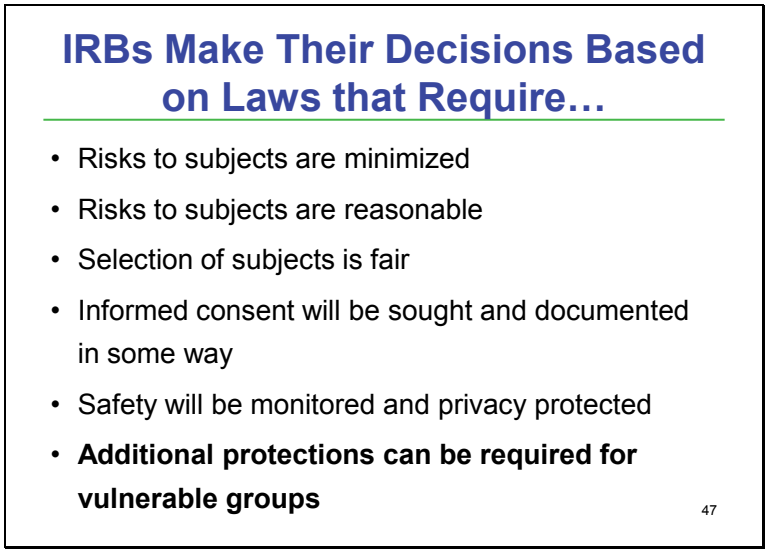

Reasonable risk is measured in part in relation to anticipated benefits and importance of knowledge

Vulnerable groups include children, prisoners, pregnant women, mentally disabled people (including those with dementia), and economically or educationally disadvantaged people.

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Basic Elements of Informed Consent Disclosure

- Purpose and nature of research
- Foreseeable risks and discomforts
- Reasonably expected benefits to subject or others
- Alternatives available to subjects
- Extent of confidentiality of information
- Availability of compensation for injury
- Person to contact in case of injury
- Right to refuse to participate or to withdraw

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This is the minimum that researchers have to tell people who they are recruiting into their studies before getting their consent.

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How Is Surrogate-Based Clinical Research (SBR) Currently Regulated?

Current Practices and Issues

- Determining competence
- Degrees of impairment and the ability to consent
- What do the laws and regulations currently say?

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Determining Competence

- People with dementia are considered incompetent only if they have significant impairment of one or more of the following abilities:
  - Understanding, i.e., comprehending information
  - Appreciation, i.e., recognizing the implications of their choices
  - Reasoning
  - Making a choice

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Studies suggest that most people with very mild dementia can still meet these standards for making their own decisions. But as severity increases, the percentage of competent people declines. Most people with moderate dementia are no longer capable of making their own decisions and a substitute decision maker is needed.

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Degrees of Impairment and the Ability to Consent

- Various levels of ability exist among those with Alzheimer's Disease – Recall the video presentation
  - Early stage – Just diagnosed and still independent and probably competent
  - Mild – Can Still communicate, live at home, but has poor judgment. Is somewhat independent but probably not competent
  - More severe – Uncommunicative, bedridden, etc. Dependent and clearly incompetent
- The point is that ”incapable of consent” captures a wide range of people
  - Some are able to cooperate and talk with caregivers and researchers, yet still be too impaired to give own consent
  - Some are unable to cooperate at all

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What Do the Laws and Regulations Currently Say?

- Currently, when an adult lacks the capacity to give informed consent for research…
  - The federal regulations allow someone else—a "legally authorized representative" (**LAR**) to consent on their behalf
  - **But LAR is not defined; it is left to the states and local governments to define.**
  - **Few states have made clear who can be LAR.**
- In some studies, surrogate consent is obtained from family members, but the current legal foundation for this practice is weak in most states
- Thus, in most places, surrogate consent represents a "gray zone" of law
- Even in states that have surrogate consent laws, IRBs still have the authority to approve or deny permission for the research or use of surrogates

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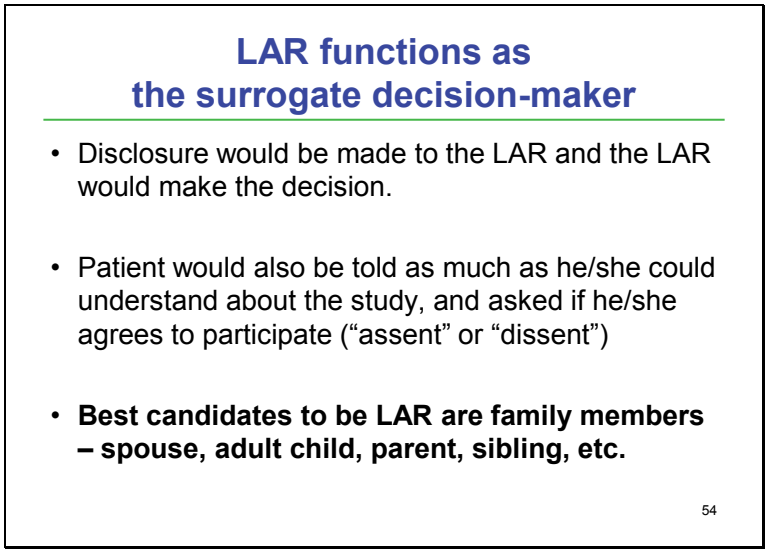

There are advantages to using family members as the LAR, but some disadvantages as well.

Advantages:

- Family members are likely to be readily available;
- They are presumed to care about the interests of the impaired person;
- Family members are most likely to know what the impaired person himself or herself might have wanted to do in this situation;
- Appointment of alternative decision makers, such as legal guardians, is likely to be time-consuming and costly, and will only rarely be pursued.

Disadvantages:

- Family members are likely to have no particular background in science/medicine—may have a hard time understanding what the study is about, and the risks and benefits of the patient’s participation
- There could be a conflict between the family member’s interests and the patient’s interests, e.g., if a monetary incentive is being offered for participation

But on balance, family members are the best candidates for the role.

Should a patient object to continuing in a study, even if he/she were not considered competent to decide on participation in the first place, the person’s participation would be ended. If treatment were required, it would be provided outside of a research project (i.e., ordinary clinical care).

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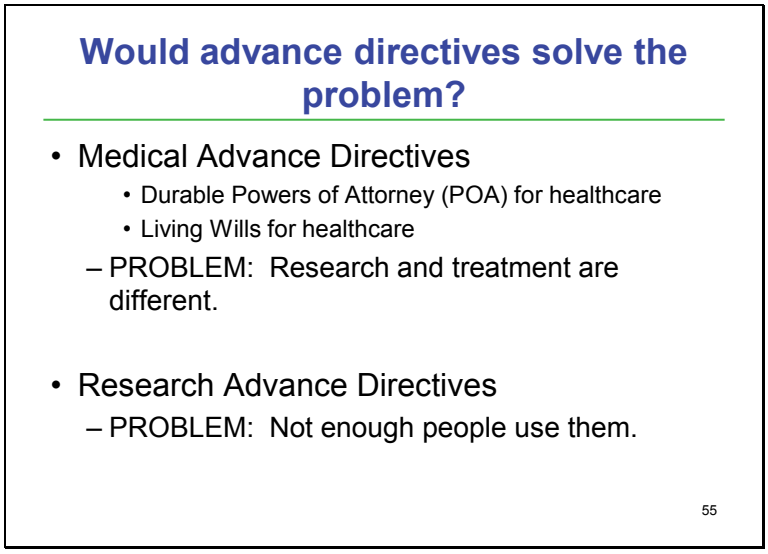

Advance directives allow people to make choices about their medical care in the future, should they become unable to make decisions for themselves at the time.
They may take the form of:

- Durable Powers of Attorney for Healthcare – allow appointment of someone else to make medical decisions in the event of future incapacity (e.g., a spouse); or
- Living wills for healthcare – in which the person him/herself makes an advance decision (e.g., no CPR); or
- Advance directives that combine both.

In principle, similar advance directives could be developed to consent to research. But there are several problems with this approach:

- Currently, no laws provide for it;
- Difficult to anticipate the types of studies for which one might be eligible;
- Unlikely that many people will complete them.

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Ethical Questions That Need Answers

Main Policy Questions

- Should family members be allowed to give surrogate consent (that is to act as the LAR)?
- If so, for what types of research?

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Reasons in Favor of Surrogate Consent for Research

- Importance of advancing knowledge about disorders that impair thinking, such as Alzheimer's Disease
- If potential research subjects designate a surrogate decision maker in advance, abiding by that person's judgment respects the subject's autonomous choice
- If families are already allowed to make life/death treatment decisions for incapacitated loved ones, they should be given authority for research consent too.

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These arguments are based on the principles for regulation of research that we discussed earlier:
Advancing knowledge is an aspect of beneficence, though towards third parties and not the patient/subject.
Respecting autonomous choice is a reflection of respect for persons.

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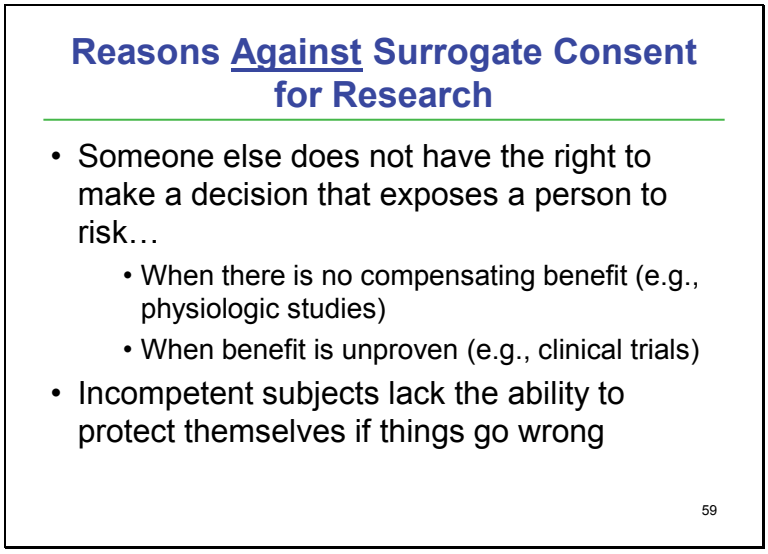

Example of study without prospect of benefit: fMRI (i.e., brain scan) study in a person with Alzheimer's Disease.

Example of study where benefit is unproven: clinical trial of new medication to see if it slows down the progression of Alzheimer's Disease.

Example: A person too confused to recognize that the headache they are suffering may relate to the study in which they are enrolled may not tell the researchers, who may not know about the adverse effect until permanent harm has occurred.

Questions To Be Resolved Regarding Surrogate-Based Research - 1

- Should we let a family member or someone else make the decision for someone who is too impaired to make a decision for themselves about entering a research project?
  - If we say no, what is the likely impact on research in dementia and other disorders that affect the mind?
  - If we say yes, how can we best protect the autonomy and safety of our research subjects?

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Questions To Be Resolved Regarding Surrogate-Based Research - 2

- If we say surrogate consent can be permissible how should we limit, if at all, the scope of the authority we are willing to give surrogates?
  - It's permissible but only if the subject is likely to have some benefit in participation from participation in the study?
  - It's allowed for minimal risk research only?
  - Only if the patient had an advance directive specifically for research participation?

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What are the consequences of each of these limitations?

- If limited to research with some prospect of benefit to subjects, studies of the basic mechanisms of illnesses like Alzheimer's Disease would be excluded (e.g., imaging studies of the brain), thus slowing down the development of knowledge that might be needed to develop effective treatments. And many such studies only represent a small degree of risk to subjects.
- If limited to minimal risk research, among the studies excluded would likely be many studies of new treatments for Alzheimer's Disease, since the side-effects associated with many new medications are usually considered to represent more than minimal risk.
- If we require that subjects have designated a surrogate decision maker in advance, the reality is almost certainly that few people will do this, meaning very few additional subjects would be available for research studies.

Approximately 15% of the population has advanced directives, even though the likelihood that we will all need a directive for medical treatment at some point is very high. What percentage will have one for research purposes? Not a solution to the overall problem.