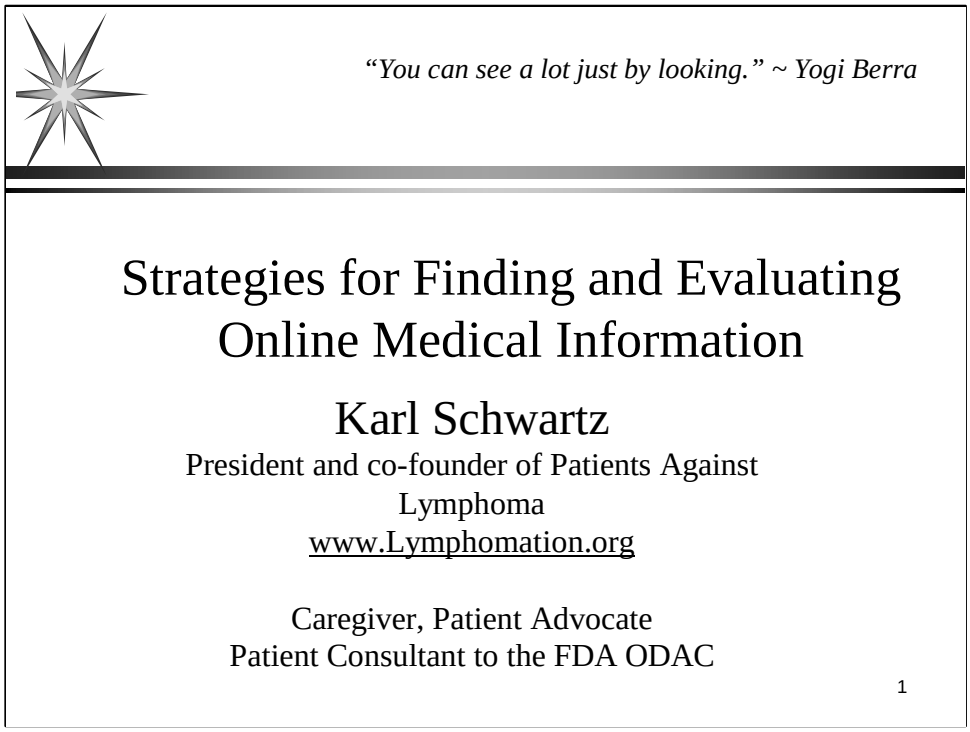


Good evening,

I did not plan on doing this work.

My spouse, Joanne, was diagnosed with lymphoma in 1996.

Before that life-altering event, we authored and designed books on personal computers.

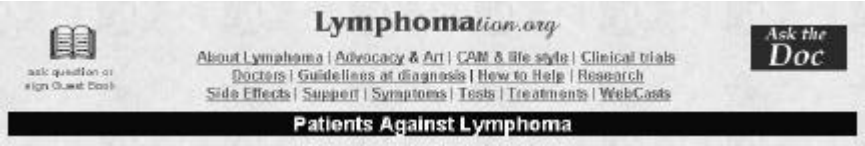
My formal background is in fine arts; and I've been a teacher.

Like others, I turned to the Internet to find answers to basic questions with a hope that knowledge might replace our fear.

What is lymphoma? What are the treatments? Is it curable?

Patients Against Lymphoma

- Founded in 2002 | Independent of health industry funding | Patient-centered
- Why? We needed a place to put content that answered frequently asked questions, and links to credible resources



www.Lymphomation.org

2

This slide introduces how our non-profit group, PAL, came to be.

As you may know, many online support groups emerged spontaneously on the Internet

Before long the need for a website to put frequently asked questions became apparent.

We named it Lymphomation.org

We evolved into a group that does more than that.

Patients Against Lymphoma

Helping patients to think like scientists; and scientists like patients.

- Evidence-based information on lymphomas
- Evaluating medical claims and data
- Focus on clinical trials:
  - Locating
  - Design of
  - Trials of interest

http://www.lymphomation.org/clinical-trials-gov.htm

3

Our primary objective is to help patients and caregiver locate information about lymphoma and its treatments, and also to help our visitors evaluate information critically.

We do not raise money for research. We are a volunteer-based organization. Our board members are caregivers or patients. Many of our advisors are scientist directly affected by the disease.

Much of our work is focused on clinical trials: making studies easy to find, evaluate,

… and sometimes we critique them, if the study appears unethical, for example

We are independent of heath industry funding. Thus, we can speak freely and with greater credibility about clinical trial design, and highlight trials of interest without having a financial conflict of interest.

The Dark Side of a Miracle

- **Miracle:** that we can call up so much information almost instantly within a rectangle in our homes.
- **The Dark side:** much of it is of questionable value; might appear convincing …

4

The Internet is a marvelous tool, but it can also be the source of low quality information and sometimes harmful errors and deceptions.

Here's what I thought we might cover this evening:

Some of the benefits and risks of doing your own research;

The important issue of trust: Who and What to believe? What's credible?

The importance of knowing your limitations

Common sources of bias;

How to weigh sources of information

We'll try out some ready-to-use research tools on lymphomation.org that are specific to lymphoma, but can be adapted easily for other research.

…

Reasons for Caution

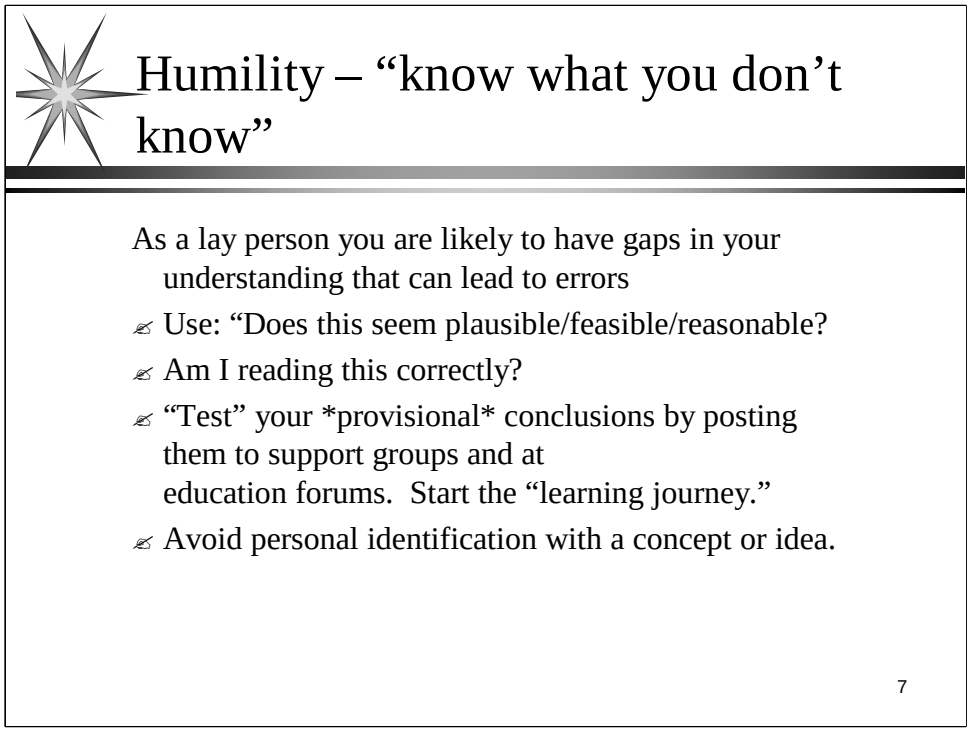
BIAS	ERROR	THEFT
Prejudging before the data is in … lack of objectivity. Financial conflict of interest, Intellectual bias Wishful thinking Ego	Conclusions based on: Poor study design, Preclinical information, Coincidence (not causal)	Intentional, Misleading for profit, Taking advantage of fear and wishful thinking

6

On this slide we list the many reasons to be cautious … about ideas, reports, and even our own opinions.

We need to develop a healthy sense of skepticism for all the reasons listed here:

Bias, Error, and Theft

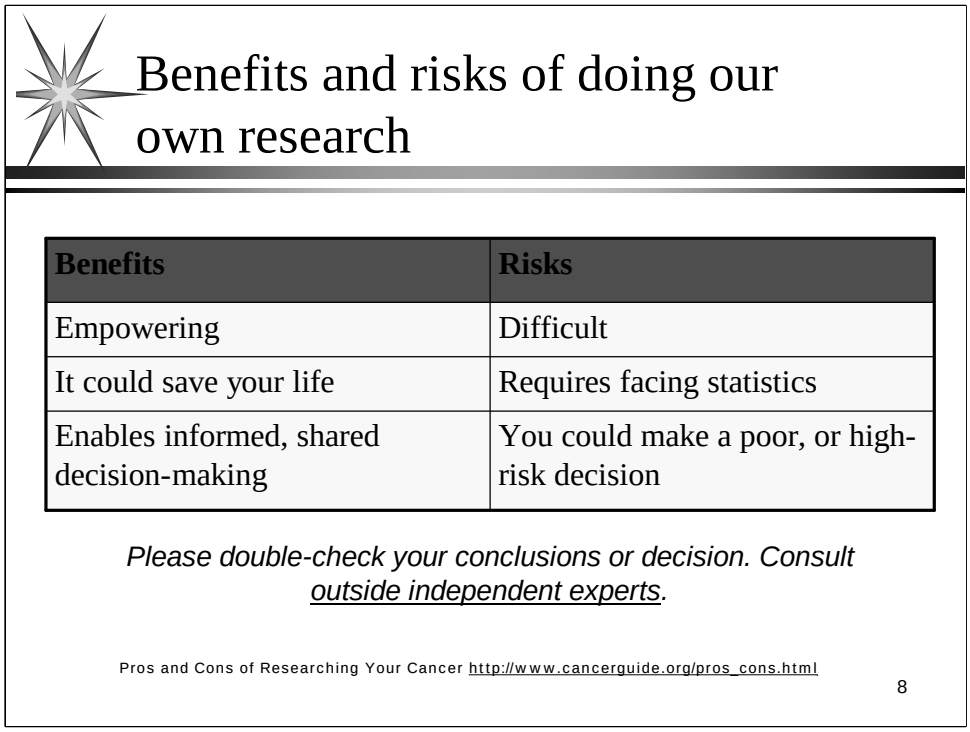


It seems that the very best scientists are often the most cautious … are most in touch with what is not known. It’s part of the discipline of science to test and to let the data speak …. not to prejudge, and to respect the complexity of biological processes.

The very best doctors and scientists understand that reliable answers are difficult to come by.

What is true is often very difficult for anyone to know.

Ironically, <u>statements of certainty</u> can often be markers of questionable information.



So what are the potential risks and benefits of doing your <u>own research</u>?

Let's start with the downside:

Research requires time and effort … learning a new vocabulary

It can be difficult to face statistics about survival

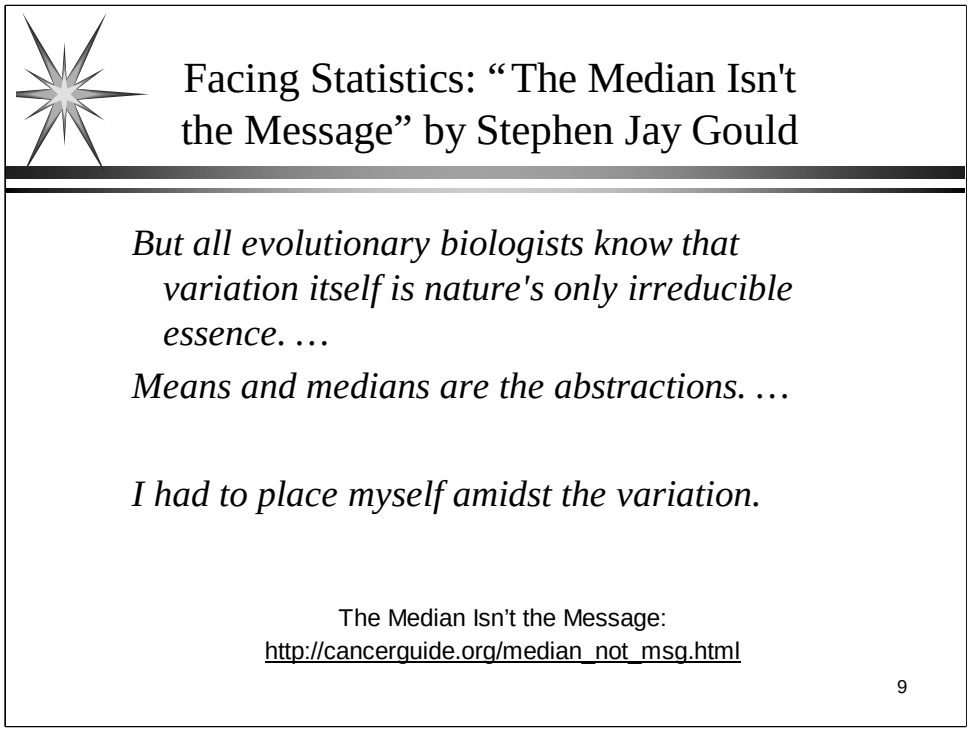
Not knowing what you don't know, can lead to wrong decision.

The positives:

Learning about the disease and the treatment often relieves fear.

Knowledge <u>is</u> empowering; it <u>can</u> provide an important sense of control.
It helps you to participate with your doctor in treatment decisions; to ask <u>informed questions</u>, which can lead to better care.

Finally, it can sometimes save a life. You might locate a study that can be more effective for you than standard approaches. For example, a targeted therapy that is less toxic;
Or a therapy that works with a unique mechanism that overcomes drug resistance.



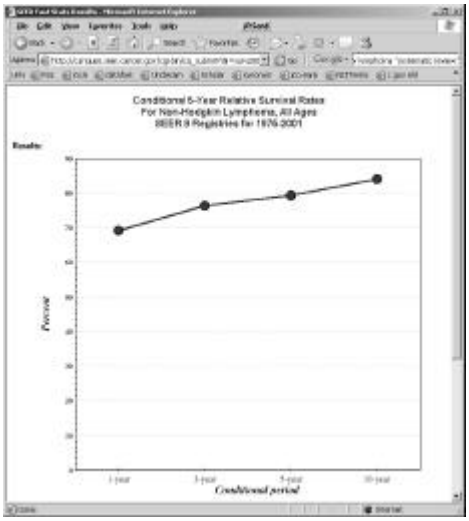
Facing statistics can become a little easier when you know the limitations;

that it's a calculation on a broad population,
which can't account for individual differences,
and changing circumstances.

The calculation of the average survival is based, necessarily, on past data and older approaches.

It takes time for data to mature, and to capture and evaluate new data using new treatments.

Conditional Survival: NHL



"Percent represents the probability of surviving 5 years following the conditional period."

…

… an additional 5 years, from which point conditional survival is again recalculated.

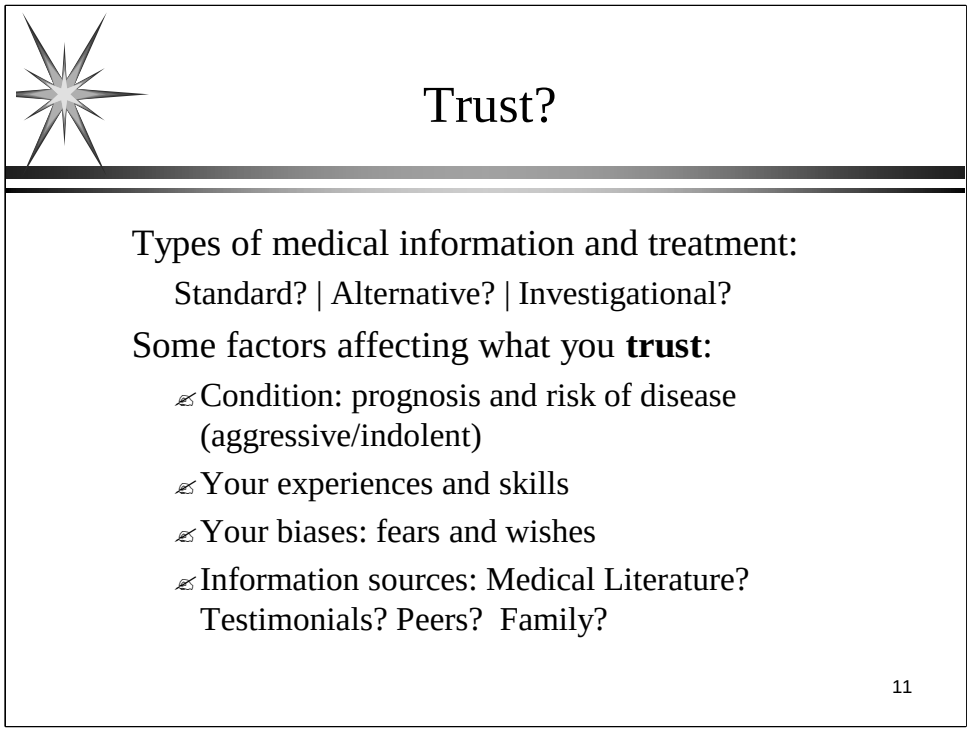
http://www.lymphomation.org/statistics.htm

This chart provided by SEER is specific to NHL, but not to any subtype (indolent/aggressive, follicular, diffuse, MCL).

I should note that PAL is advocating for subtype-specific statistics on SEER.

But it's my impression that the principle of conditional survival applies to all cancer types, and subtypes.

Just as runners who reach milestones in a race are more likely to complete the entire course than all runners at the starting line.

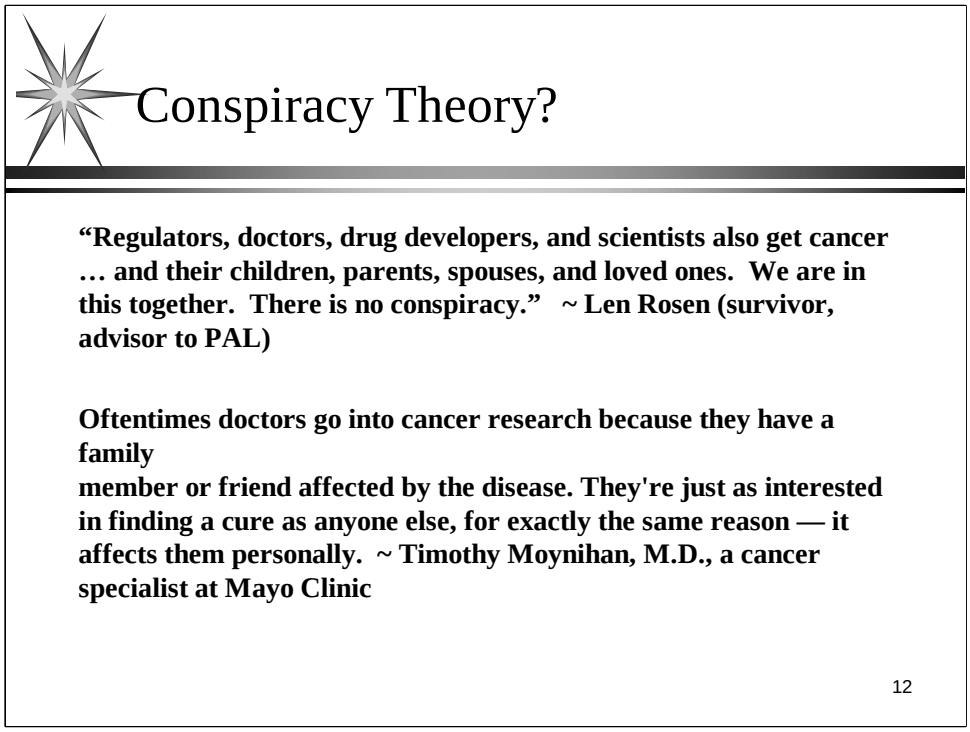


Perhaps a good place to begin the research process is to identify the basic schools or approaches.

And how reliable is the information from the various sources?

Which path we take probably boils down to a matter of <u>TRUST</u>

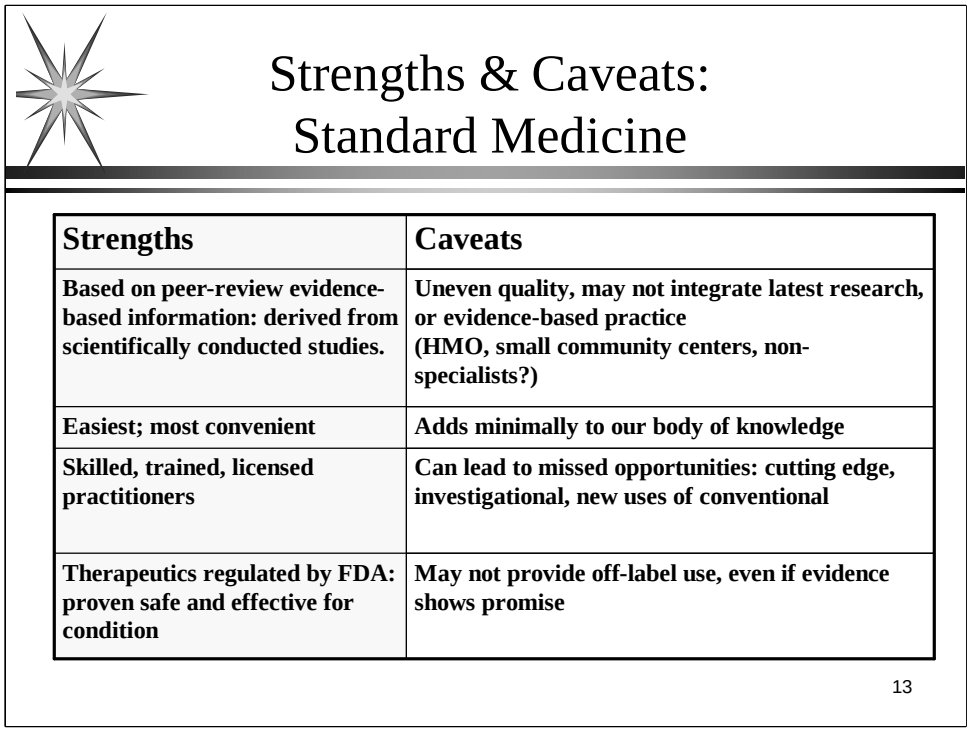
There are many factors that determine where we look for information, and what we will tend to believe….
Such as our biases, our background, and the prognosis of the condition.



I'd like to direct your attention to a myth that is widely circulated on the Internet:

That there's a conspiracy to keep cures for cancer from patients, so that drug companies and doctors can make profits.

If you are a doctor, would you keep silent about a conspiracy, or a rigged system of drug evaluation, if your child was diagnosed with cancer? I should note that one in two men will get a serious cancer in their lifetime, and one in three women. It's in everyone's best interest to find better treatments for cancer.



Starting here, I'll outline the caveats and strengths of different approaches to cancer therapy.

Standard medicine is evidence-based, … administered by skilled practitioners,

but that the quality can be uneven.

Sometimes the latest research findings are slow to be incorporated,
particularly in community centers or HMO's

You may not know that the practice of standard medicine adds very little to our body of knowledge.

A drug's label describes the condition it may be used for, but sometimes a dug
is also effective for conditions not listed on the label.

A general practitioner might not be aware of appropriate off-label uses,
or of promising investigational or cutting edge approaches.

Strengths & Caveats: Investigational Medicine

Strengths	Caveats
Extensive preclinical research: Real potential, bioavailablity and toxicity well characterized	Most do not win approval. New is not necessarily better.
Adds to our body of knowledge	Potential for investigator bias
Participants very closely monitored by skilled, trained, licensed practitioners	Requires additional tests, procedures; travel, time
New mechanisms, potential to overcome drug resistance or improve outcome, often targeted Can save your life.	Could have unforeseen, long term risks?
FDA/ IRB: monitors conduct of study; dosing, monitoring, interim reviews …	Early phase: Sponsors may hype potential via press releases; or fail to disclose negatives.

This table shows some of the pros and cons of investigational medicine.

Each trial is unique and can have very different risk/benefit profiles. Some studies can be safer than standard approaches, but others can be very high risk.

Sometimes trials are sponsored by the NCI as post marketing studies, for example, to test a new use of available treatments: New dosing, scheduling, or treatment sequences …

I think the best advice is to consult independent specialists to help them identify investigational approaches that may be appropriate to your unique clinical circumstance.

Strengths & Caveats: Alternative Medicine

Strengths	Caveats
Often non-toxic	Lacks supporting data: relies on testimonials, cell culture or animal model activity, lacks critical peer review, not tested with controls
Can provide a sense of control	Can lead to missed opportunities: investigational, novel uses of conventional
Rarely will preclude future use of standard treatment	Harmful if it leads to delay or avoidance of effective treatments; could interact with treatments or meds?
	Can't add to our body of knowledge
	Herbs not regulated; can have inaccurate labeling, may have contaminants

15

Alternative medicine is defined as practices or products sold to patients, based on untested theories as substitutes for standard evidence-based medicine.

It's important to distinguish this from complementary medicine – practices that may augment standard medicine, or improve one's performance and quality of life.

It's worth noting that standard medicines are often derived from natural compounds – I believe that as many as 25% of cancer therapeutics come from nature, such as Vincristine from Periwinkle.

As you may know, natural does not mean non-toxic. Plants, animals, and insects are at war, and manufacture compounds to defend themselves and to kill.

Be aware that almost all advertisements for herbs as ways to fight cancer are based on cell culture and animal models.

Discussion: , preclinical models have a very poor track record for predicting clinical benefit (1 in 5,000 to be roughly exact).

Money is also made selling false hope. Yes, money is made selling

Cell culture, animal, human?

Basic kinds of studies:

preclinical

- **Cell culture** 1 in 5,000 win marketing approval. Poor model
- **Animal studies** - starting point; rarely predictive of benefit in humans
- **Human** (Clinical) evidence of clinical benefit? Phase I, II, III?
  - Activity often does not = clinical benefit.

Product Pipeline and Clinical Trials: Bringing a Drug to Market
http://www.biology.iupui.edu/biocourses/Biol540/4pipeline2k5.htm

16

This slide shows the basic kinds of studies. Starting with preclinical types: cell culture and animal

Words that can help to recognize cell culture experiments are:
in-vitro. cell lines, cultured, test tube, assay ….

Preclinical evaluations accounts for over 40% of pharmaceutical companies' research and development expenditures.4 On average, only one 1 of every 5,000 compounds earns FDA approval.5

The goal of clinical studies is to prove a therapy provide clinical benefit, and outweigh the risks for a given condition. Preclinical information can be interesting, but ought not be considered evidence.

Herbal Ad: Language example

Ad captured from LEF.org:

Resveratrol, a naturally occurring substance found in grapes, blocks the growth of lymphoma cells and also increases their rate of cell death (Bruno R et al 2003; Park JW et al 2001). Resveratrol sensitizes chemotherapy-resistant lymphoma cells to treatment with paclitaxel-based chemotherapy (Jazirehi AR et al 2004). Resveratrol also reduces the production of growth factors such as VEGF and IL-8 , and theoretically should be beneficial in reducing the ability of lymphoma cells to spread to other organs (Dulak J 2005)."

Here's an ad copied from the Life Extension foundation. LEF.org

Is it convincing? Does it seem credible because it cites scientific studies?

Herbal Ad: Not said

Not described in Ad:

- **Cell culture studies are poor predictors of efficacy in the body**
- **Bioavailablity? how the compound is affected by digestion (does it reach blood?)**
- **Effective dose? If it reaches blood, how much do you have to ingest to get doses equivalent to the cell culture experiments?**

Resveratrol is an interesting compound, no question, and safe, but:

But the studies are all preclinical and as such do not account for bioavailablity – how the compound is affected by digestion, nor does it account for dosing – how much of the compound you need to take to get an equivalent dose?

While LEF describes itself as a scientific foundation, it basically sells vitamin products,
and the language of the ads - are clearly biased.

These are aspects of an herb's potential that are painfully absent from ads on LEF.org, for example. Instead they use conclusive language.

Research Tools

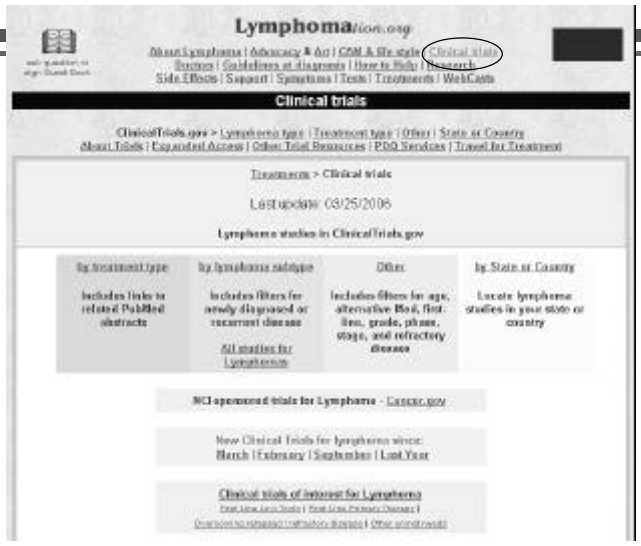
Ready-to-use: http://www.lymphomation.org/research-tools.htm

We provide ready-to-use queries (search commands) of credible resources on our Research page.

Let's take a quick tour:

- **Refining the search**
- **Changing the keywords**
- **Going back**

Research Clinical Trials



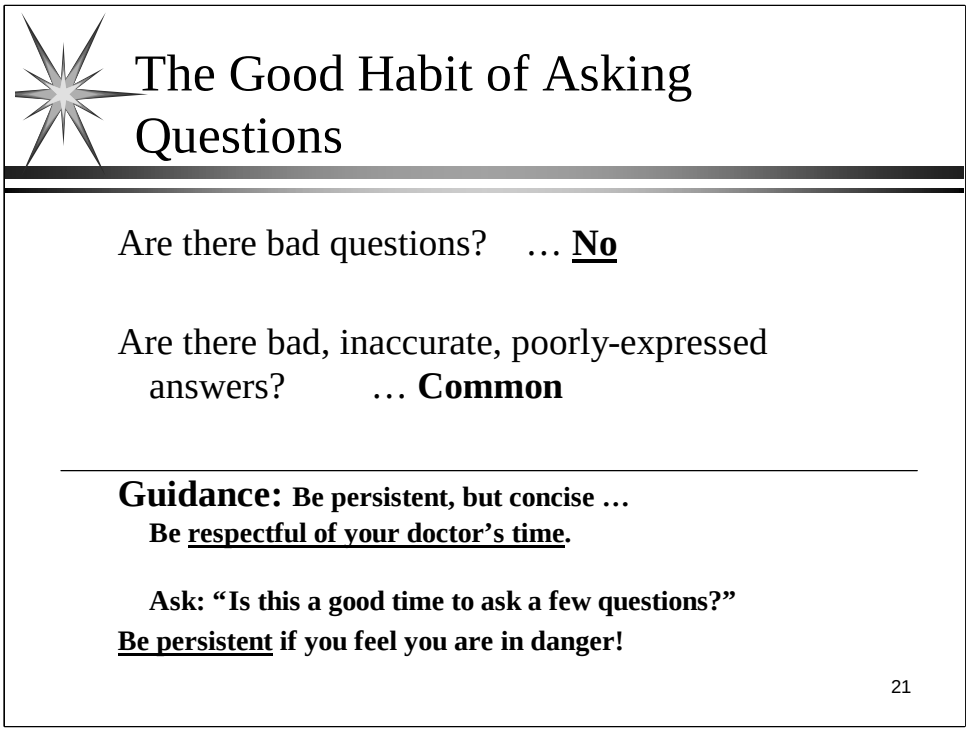
http://www.lymphomation.org/clinical-trials-gov.htm

This slide shows a screenshot of our clinical trial locator

From here we provide ready-to-use queries of ClinicalTrials.gov, a comprehensive database of clinical trials.

The FDA has mandated that all studies for life-threatening conditions be posted here.

Let's take a quick tour:



There's always a gap between what we know, and could know.

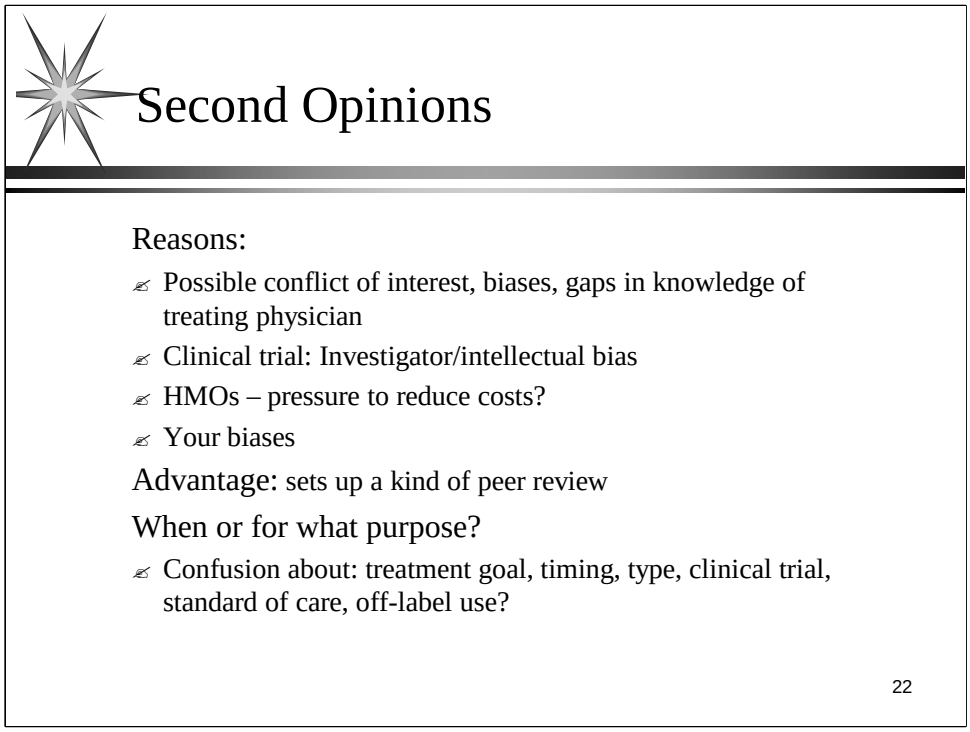
I think the very best scientists are in touch with this boundary; and with asking very basic questions.

Good doctors will want to answer your questions, but may not always have sufficient time.

Inquire if you may ask question by email, or fax, so that you are not interrupting a consult with another patient, or delaying a medical intervention.

However, be persistent if a symptom or side effect might require prompt attention.

When discussing a clinical trial, it is required that we have full understanding
of the risks and benefits of the study, and of all alternative standard approaches.
Don't allow yourself to be rushed, or to have unanswered questions.



Why should we consult outside experts?

Even trained oncologists can have conflicts of interest, biases, or gaps in knowledge
- <u>especially if he or she does not specialize in lymphomas</u>.

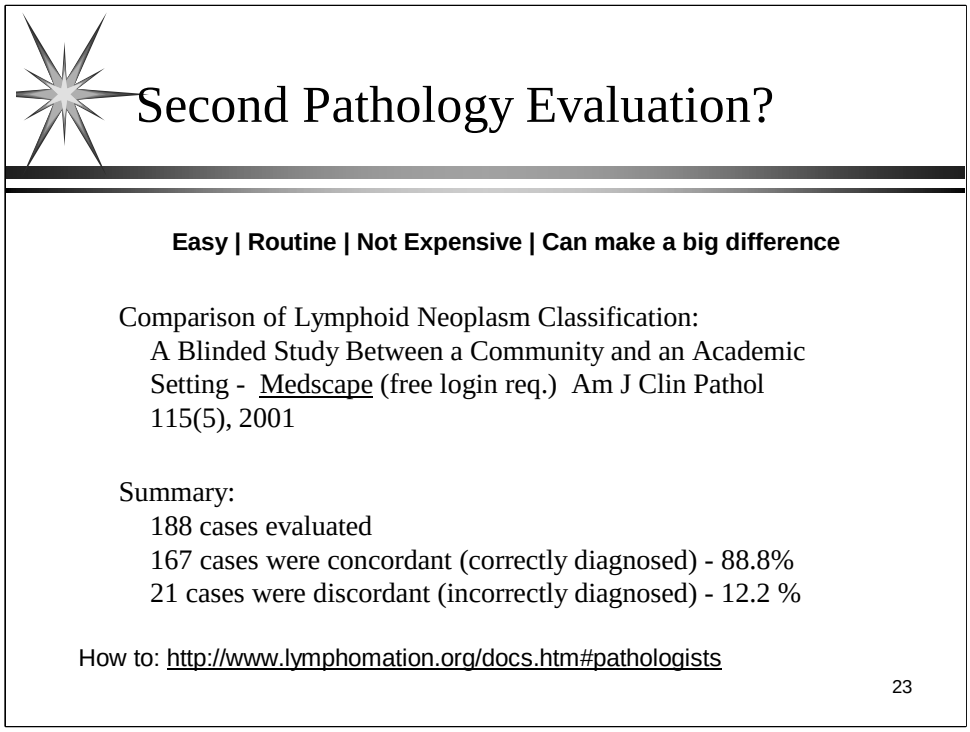
A community doctor might have a bias in favor of what is <u>easiest to administer</u>.

Investigators may have an <u>intellectual bias</u> about a therapy they have fostered.

An <u>HMO</u> physician may work under pressures to <u>cut costs</u>.

A second opinion sets up a kind of <u>peer review</u>, providing a greater incentive, I think, for your doctor to be more focused on your care and the decision process.

The good doctor will encourage an expert second opinion, and will be willing to carry out his or her recommendations, when possible ...

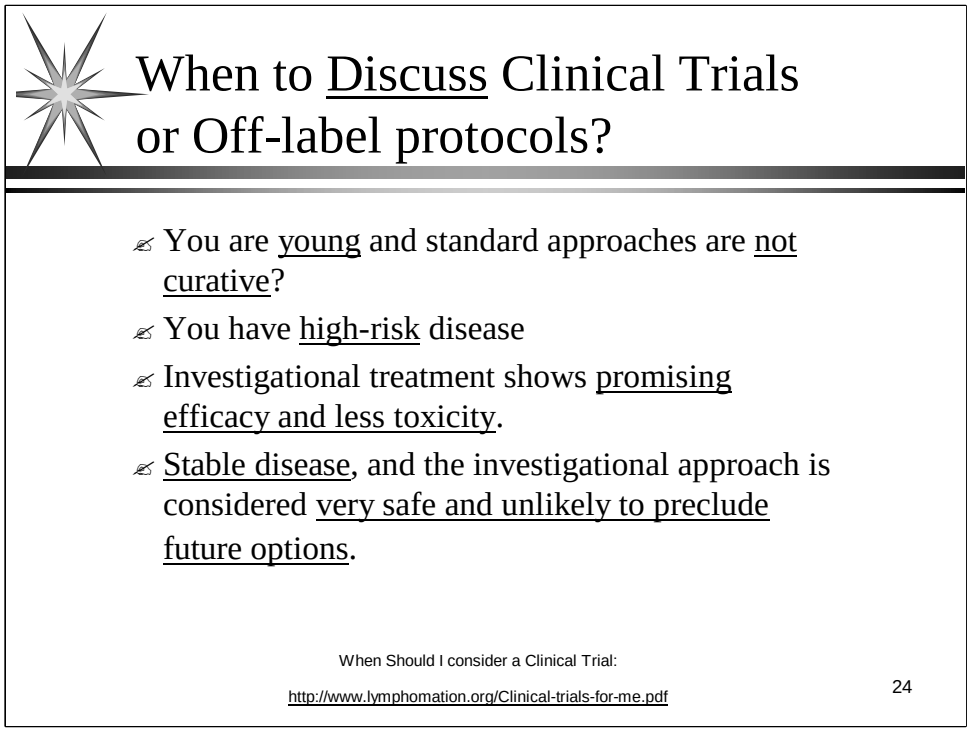


Why should we get second evaluations of biopsy tissue?

One reason is that the initial diagnosis is not always correct, as shown here.

Furthermore, according to a lymphoma specialist, Dr. John Leonard, MD:

"… gray areas exist when you see follicular and diffuse lymphomas, and you are trying to decide if transformation has occurred and whether you need to use an anthracycline — this is an area in which I would encourage a second opinion from the pathological standpoint."



Obviously, clinical trials are not appropriate for everyone, or every situation.

Here we provide a list of circumstances that may make participation reasonable, and perhaps more appropriate sometimes than standard treatment.

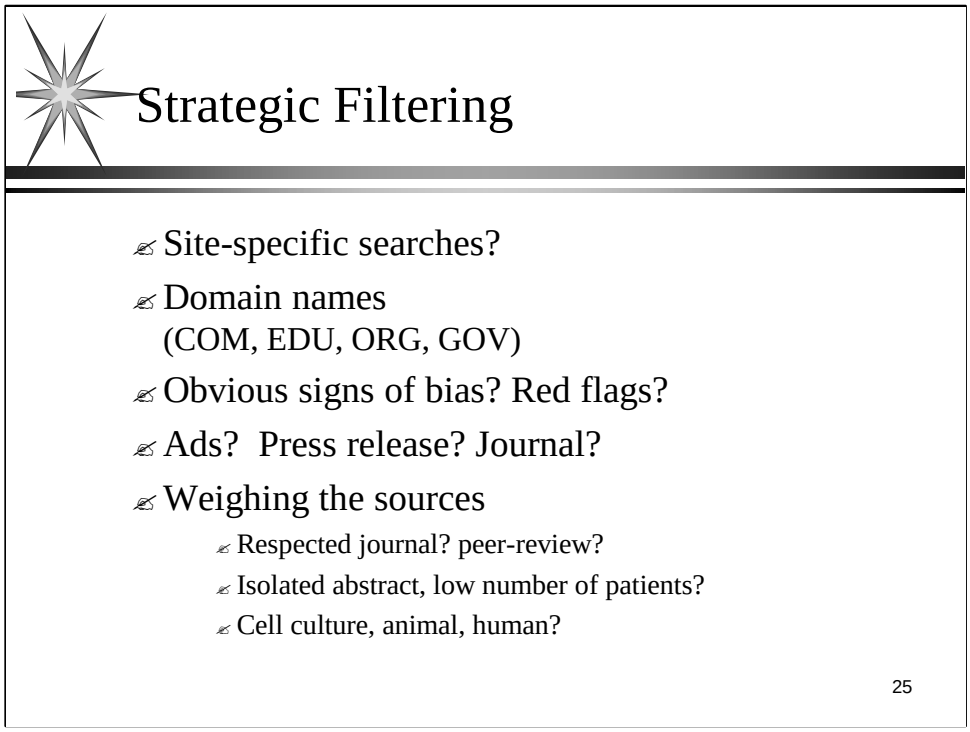
You may have high-risk disease, for example. Or there could be a very safe study you are eligible to try when you have stable disease.

The most common reason for trial participation is when standard approaches are no longer working optimally.

We recommend that you discuss investigational options with an independent expert, and not rely solely on the opinion of the investigator who can have a bias or conflict of interest.

You do not need permission from your treating physician to review or participate in clinical trials.

DISCUSSION: ==



One way to filter out the noise, the low-quality data, and bogus information, is to search the sites that provide more credible information, such as peer-reviewed reports.

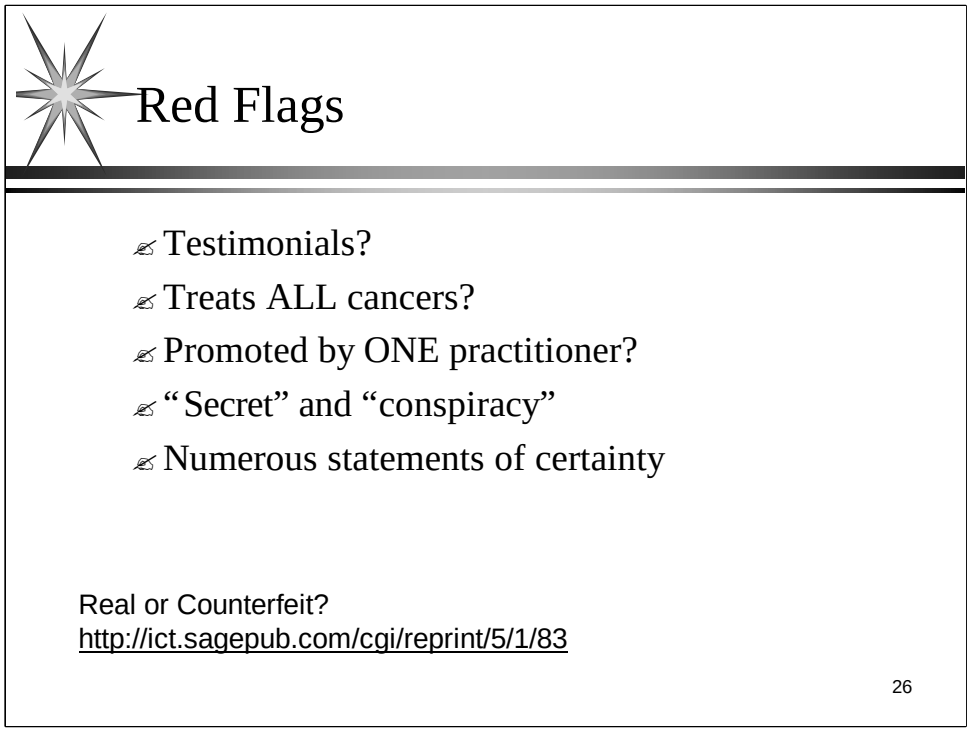
You will learn to ignore sites with obvious signs of bias, such as use of conclusive unorthodox statements.

Domain extensions tell you the type of resource, whether its government (GOV), academic (EDU), commercial (COM), foreign (UK), non-profit (ORG).

Press releases may contain misleading, overly simplified headlines – the goal is to grab your attention.

Drug sponsors sometimes feed stories to the press to put an investigational therapy in a good light.

I think it's worth noting that salesmen can seem very authentic and scientific sometimes.

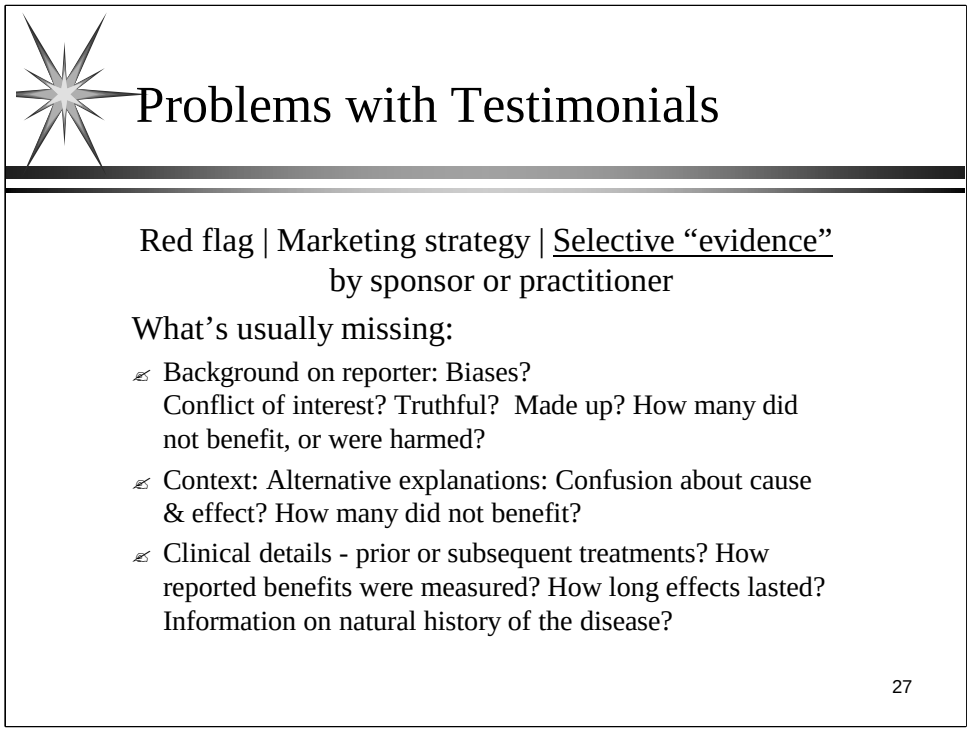


Here's a list of red flags: markers of questionable and misleading information.

But as noted before, reports on unproven practices can look genuine, like papers published in medical journals.

Discussion on link:

What looks suspicious to me are the references, none of which are specific to pancreatic cancer.

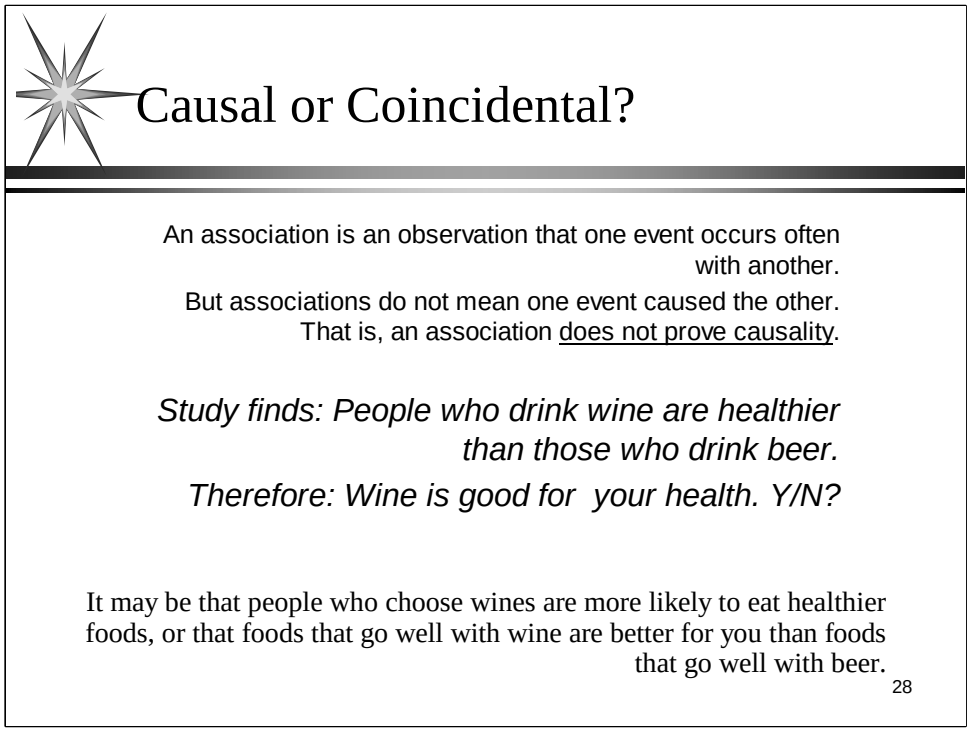


There are many problems with testimonials, summarized here.

They don't provide the clinical context, and they are selective by definition:

We don't know from a testimonial how many did not benefit, or were harmed?

We can't know if it comes from bias, error, or if it's deliberately misleading.



Here's just one example of how easy it is to arrive at false conclusions.

Lets say a study finds that people who drink wine are healthier (on average) than people who drink beer.

That is, there's an association between good health and drinking wine, relative to people who drink beer.

Can we conclude that drinking wine is good for your health?

Not really. it may be that people who choose wines are more likely to eat healthier foods (culturally?), or that foods that go well with wine are better for you than foods that go with beer: pizza and potato chips.

Causal or Coincidence? Natural history?

- For **indolent lymphomas** - easy to confuse cause and coincidence. The ***Variable natural course -*** can remain stable for many years without any intervention, or regress spontaneously

  "… as many as 20% to 30% of patients will experience regressions at some time in the clinical course of their disease." **1**

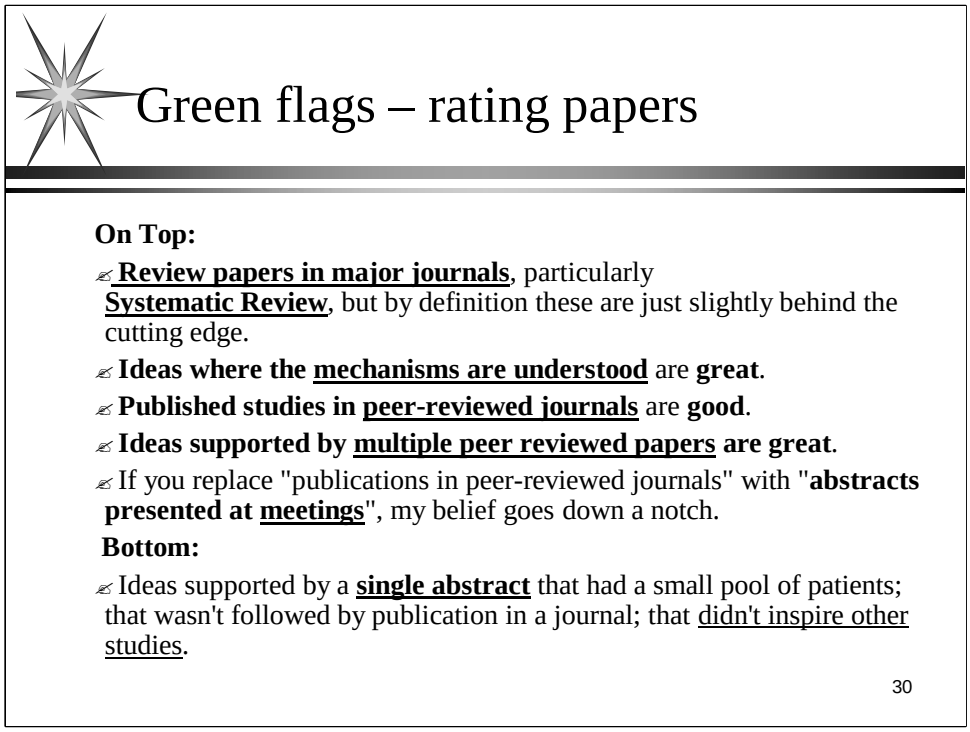
- If 1000 patients with indolent nhl try a supplement, as many as 300 (30%) are likely to do well because they would have done well anyway. This "effect," - which has good probability of being unrelated to any practice - understandably can result in strong belief, and promotion.

1. The natural history of initially untreated low-grade non-Hodgkin's lymphomas. N Engl J Med. 1984 Dec 6; 311(23): 1471-5. PMID: 6548796

This factor – the variable natural history of the disease - also influences the design of clinical studies for indolent lymphoma, requiring larger studies, more time, and well-designed controls.

Spontaneous remissions can occur in many cancers, and are in very common in indolent lymphoma.

Long periods of stable disease may also occur.

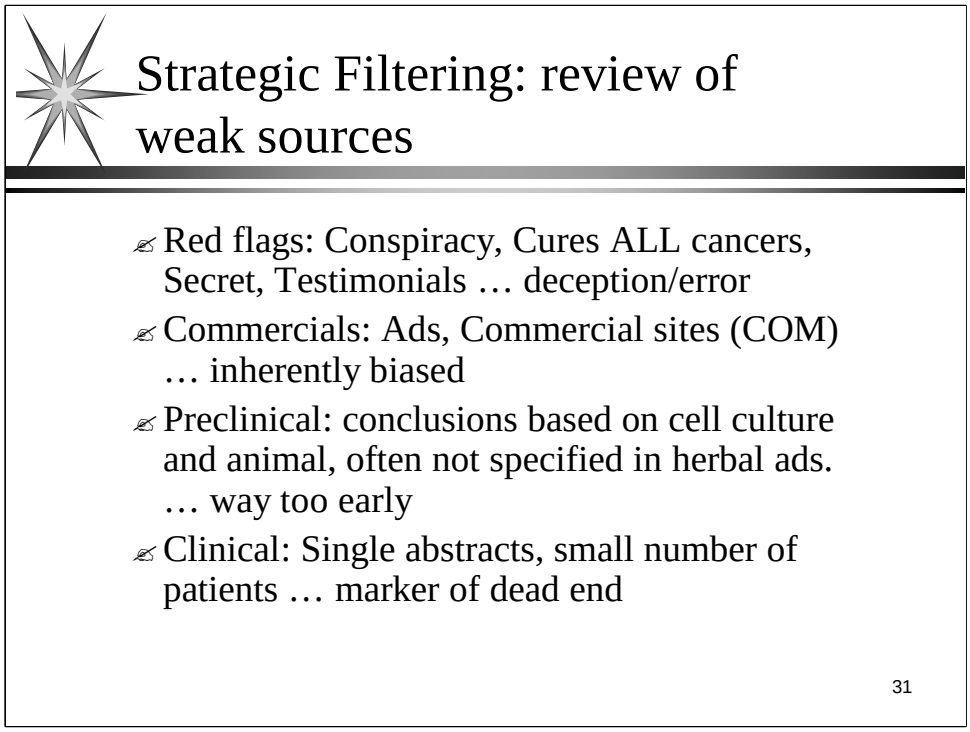


Here is a list of the most credible sources of information, provided by Andy, scientist, and advisor to PAL

At the top are review papers in major journals, particularly, systematic reviews -
an analysis of multiple studies done in a comprehensive way.

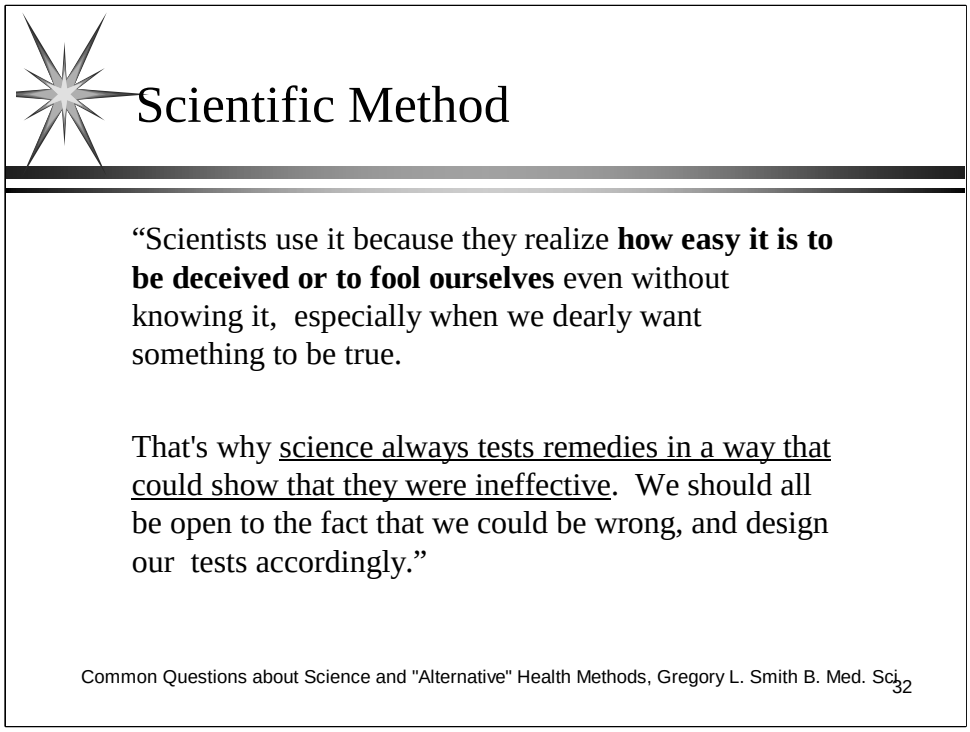
At the bottom: Single abstracts that did not inspire other studies.

DISCUSSION: Regarding the understanding of mechanisms (how the agent works), I think this becomes relevant only when the agent has proven itself to be safe and effective in clinical trials. This then drives research to understand why, so
that the drug can be improved on, or enhanced by other therapies, or use of it expanded to new conditions



Here we list the <u>least promising</u> sources of information.

Not all commercials are misleading, but ads are inherently biased. Recall that ads for herbs often cite preclinical studies.

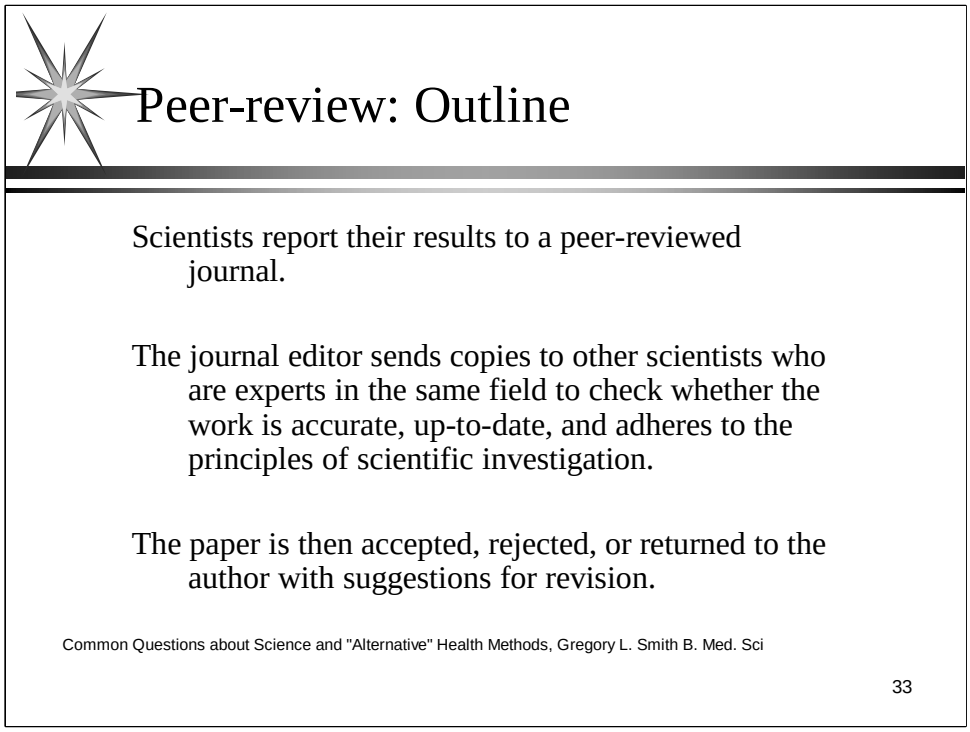


Why is scientific method so important? Why can't we rely on observation?

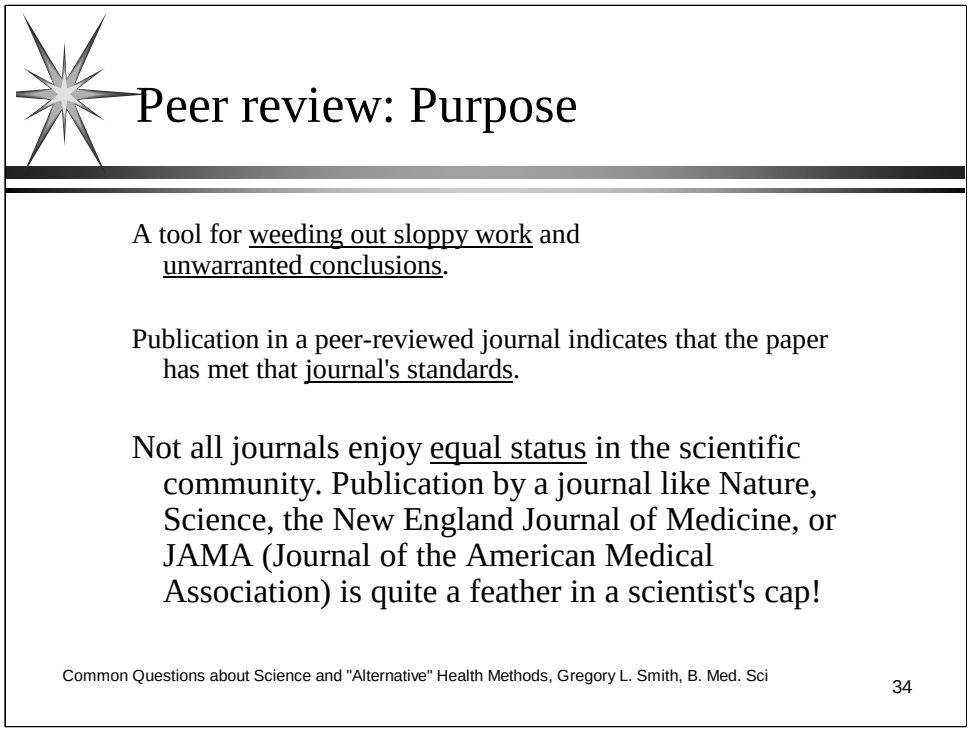
You may be aware of the HRT studies that disproved the expectation that hormone replacement was safe and effective for many conditions.

The controlled study clearly showed that anyone, even medical doctors, can be mislead by expectations and observation.

Scientific method, such as controlled studies, are the best way we have right now to test ideas and drugs. Absent these tests patients would be in greater risk, and scientific progress would be delayed by building on false assumptions.

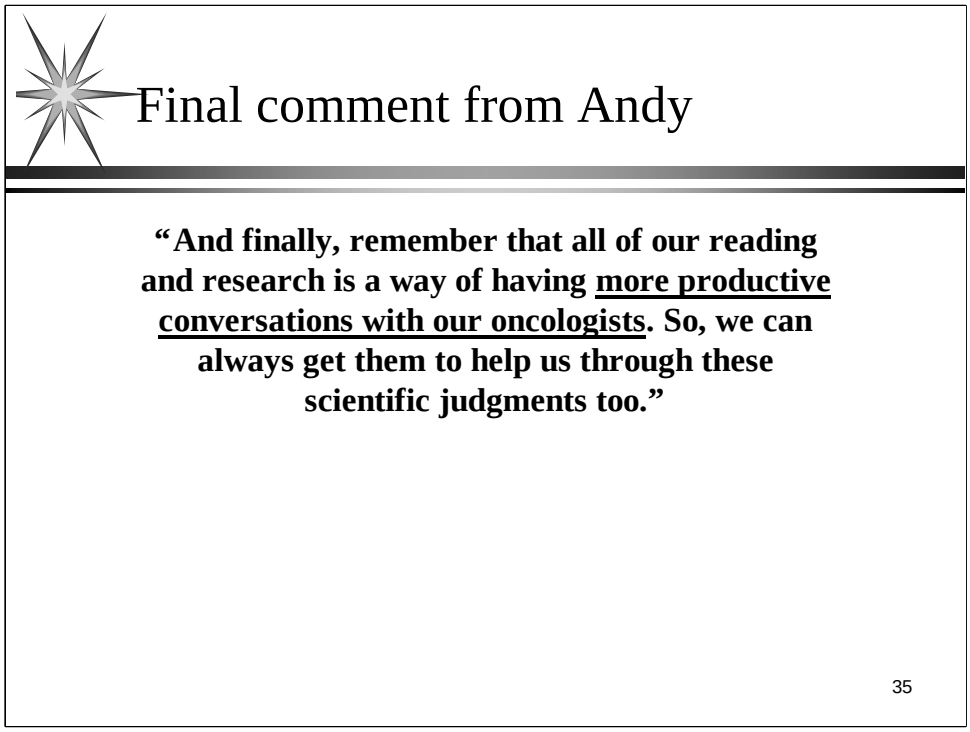


Here's an outline of the peer-review process, which checks that findings are accurate,
and adhere to quality scientific methods that eliminate bias and error.



The peer-review system is not perfect, but it's very good at protecting against shoddy work.

As noted, not all journals have the highest standards



Andy is a valued advisor to PAL. He's a scientist and newly diagnosed survivor of indolent lymphoma.

I've decided to end this talk with his wise35 comment:

And finally, remember that all of our reading and research is a way of having
more productive conversations with our oncologists.

So, we can always get them to help us through these scientific judgments too."