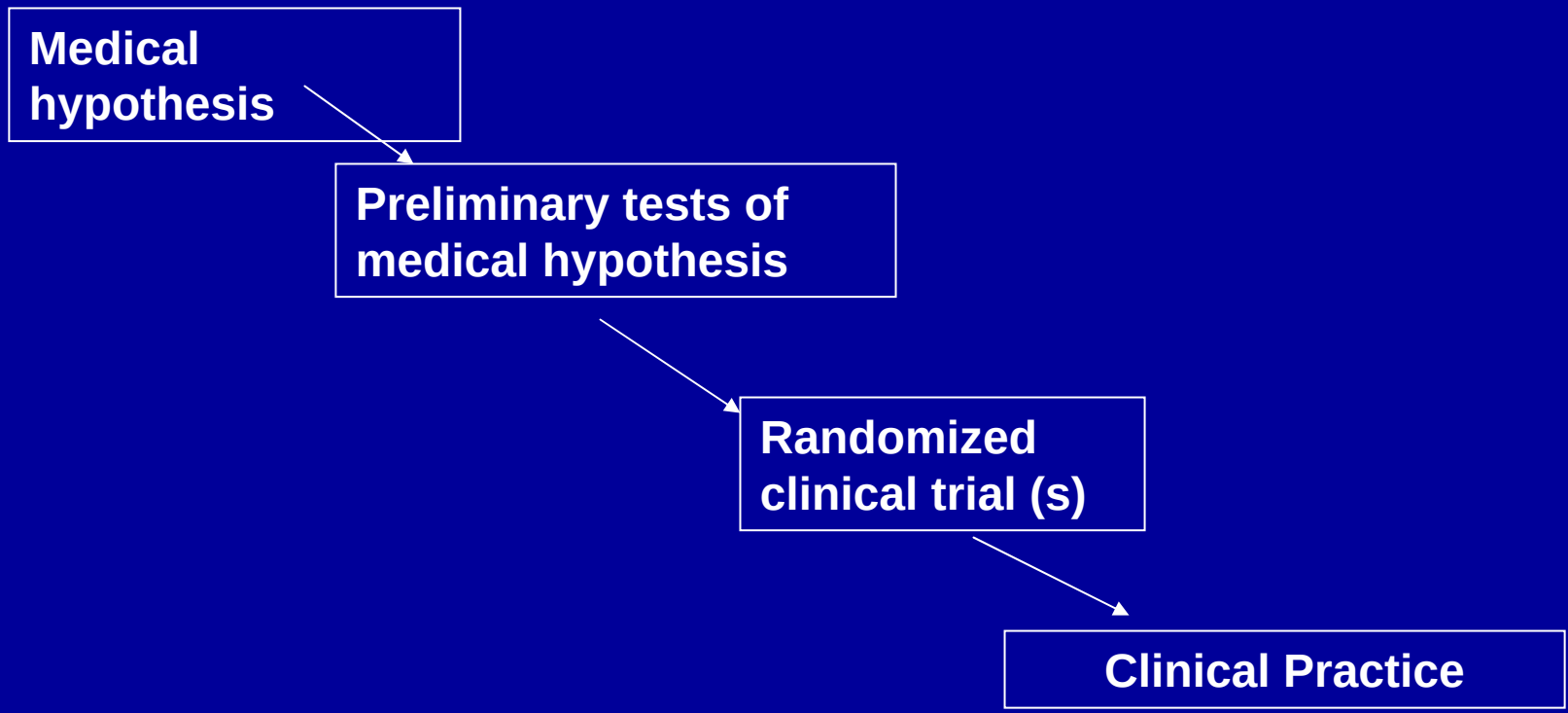
Third Party Payment: Effect on clinical trials and evidence base.

Walter J. Koroshetz, M.D.

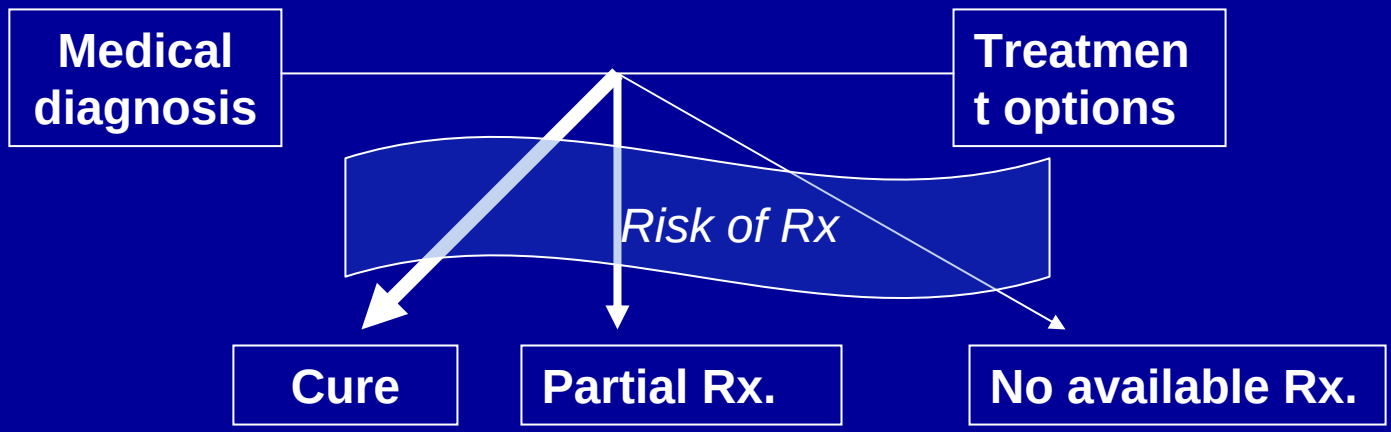
Deputy Director

National Institute of Neurological Disorders and Stroke

The policymakers viewpoint: Best case scenario

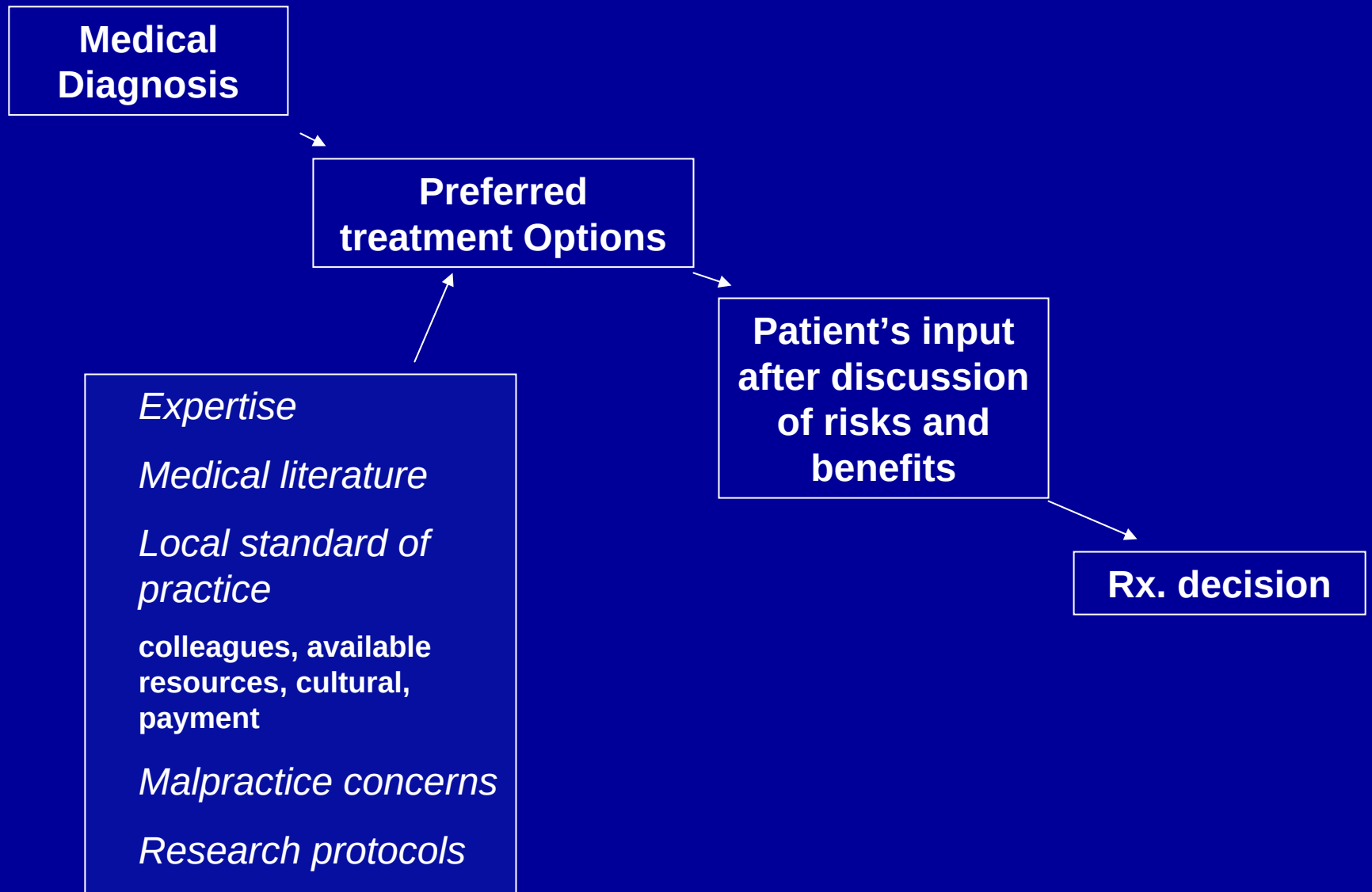


The patients perspective.



The patient rarely asks about the level of evidence except to ask what are my chances, doc?

The doctors perspective.



A good system but …when things can go wrong.

- Patient's response to diagnosis is to ignore risk.
- Physicians Rx. decisions affected by considerations related to individual success.
  - Financial, Academic gain, Political, Psychological.
- Wide gap in available medical evidence on best Rx.
  - Under this condition then harm due to 1 and 2 can be magnified.
- Available medical evidence is incomplete and suggestions based upon trend is wrong.

Extracranial-Intracranial Bypass Surgery

- Operation described in 1969
- 13 surgical series included 1,464 patients insufficient to conclude benefit
- RCT NIH funded trial of 1,377 patients showed no benefit.

Federal Register 1990 Apr 10;55(69): 13321-4

- This notice announces the Medicare program's intent to withdraw Medicare coverage of extracranial-intracranial (EC-IC) arterial bypass surgery when used to treat or prevent ischemic cerebrovascular disease of the carotid or middle cerebral arteries. Available evidence does not show that this surgery is effective.

Jennet B. Int J Technol Assess Health Care. 1989;5(3):443-57.

- “Carotid endarterectomy and EC/IC bypass grafting have been widely adopted for patients considered at risk from stroke, without good evidence of efficacy. Unjustified claims for surgery usually derive from overestimating the dangers of the disease without surgery, while perioperative risks are underestimated. Inadequate follow-up and choosing irrelevant outcome measures often add to the confusion. … Had there been a reliable data base, the efficacy of these two operations could have been determined much sooner, and inappropriate diffusion might have been prevented”.

Example: Closure of patent foramen ovale (PFO) in stroke patient.

- 28% of persons have PFO
- Clot traveling from venous system through PFO is a known cause of stroke.
- 20-40% of strokes with uncertain etiology
- 100,000's of patients per year with stroke without clear etiology have a PFO.
- Should they have their PFO closed to prevent a second stroke?
  - Depends on who they talk with???
  - Depends on whether CMS covers PFO closure.
- In majority of cases need RCT data in relevant population in order to guide decision.

Example: PFO closure.

- We don’t know the answer. You can enter a trial and have 50% chance of PFO closure or a 50% chance of just taking aspirin (which doesn’t prevent venous embolism) and we will see. Or I can close your PFO next week. There are risks, but most people walk out of the hospital the same day.
- Slow and possibly biased trial recruitment.

Example: PFO closure for secondary stroke prevention.

- “Medical treatment for these processes is often considered inadequate and mechanical closure of the PFO is an attractive, albeit controversial, alternative. PFO closure has become common practice in many centers, although recent guidelines limit its indication to certain subsets of patients”.

PFO closure for prevention of secondary stroke.

- 1000s of patients undergoing PFO closure under HDE
- “enrollment has been slow to the point where sponsors have said it is not feasible to complete a randomized study “

FDA withdraws humanitarian device exception for PFO closure devices (Oct 2006)

- FDA recently notified two manufacturers of its intent to formally propose to withdraw the HDE marketing approvals for two patent foramen ovale (PFO) occluders previously approved… .
- After FDA's most recent review, FDA concluded that the patient population described by the approved indication is significantly in excess of 4,000 patients in the U.S. per year. This finding means that these devices are no longer eligible for HUD designation and therefore, no longer eligible for marketing under an HDE.
- There are several ongoing clinical trials to evaluate the safety and effectiveness of PFO occluders in patients who have had a single cryptogenic stroke and have a PFO.

Example: Carotid artery stenting (CAS)

- CEA- value well established by RCT, but spread outside of trial population and actual value in current practice unknown.
- CAS- new technique, attractive in patients at high surgical risk. Politics complicated because non-surgical specialists competing for the first time for this population.
- RCT in this population shows at least equivalence to CEA. But in the RCT the risk of both CEA and CAS exceeds recommended limits for asymptomatic patients (80% of pts in the trial).
- Market for CAS is primarily in asymptomatic patients.
- NIH RCT CEA vs CAS in progress for less-restricted patient group. Recruitment impaired by multiple mechanisms to obtain payment for CAS. Approval by CMS would preclude successful recruitment.
- Politics and medical evidence are blended together to create “guidelines”, “position paper”.

Example: clot retrieval device.

- Endovascular devices for removal of foreign body previously approved.
- A device approved to remove foreign body is shown able to remove clot from the intracerebral artery of acute stroke patients.
- Device approved, payment approved.
- No evidence that attempt to retrieve clot leads to improved outcome in stroke patients.
- We can try to go in and get the clot or just see what happens?
- NIH trial of randomization to clot retrieval vs. supportive therapy unable to recruit.

Third Party Payment: Effect on clinical trials and evidence base.

- Proposal.
  - CMS, FDA and NIH coordinate processes to prevent major public health hazard due to premature approval of devices, drugs.
    - NIH clinical trials responsive to needs of public as reflected by proposals in front of CMS and FDA
    - FDA, CMS responsive to NIH recruitment needs.

CMS clinical research policy.

- Self certification process:
  - Imbalance between self-certified human studies trial and an NIH funded trial. Increased burden of duplicate certification– NIH and then CMS.
- Potential regional differences in coverage for trials contradicts purpose of national Clinical Research Policy and complicates larger trials.
- Impact on CMS budget of expanding coverage to all self-certifying trials may be considerable.
  - spending for trials of low medical value.