Barnett S. Kramer, M.D., M.P.H.
Associate Director for Disease Prevention,
National Institutes of Health
Disclaimer
Levels of Decision Making

Level I: "Would you have this done for yourself or for someone else in your immediate family?" Influenced by one's personal experience with the disease and capacity to deal with risk.

Level II: Physician making a recommendation for his/her patients. Also influenced by prior experience, but the strength of the scientific evidence may play a greater role.

Level III: Across-the-board recommendations for a population. Must be based even more on rigorous assessment of the scientific evidence.
“Propositions arrived at purely by logical means are completely empty as regards reality. Because Galileo saw this, and particularly because he drummed it into the scientific world, he is the father of modern physics - indeed of modern science altogether.”

Albert Einstein
Analytic Framework (Causal Pathway) for Screening Tests:
U.S. Preventive Services Task Force

1. Persons at Risk
2. Early Detection of Target Condition
3. Treatment
4. Intermediate Outcome
5. Association
6. Reduced Morbidity and/or Mortality
7. Adverse Effects of Screening
8. Adverse Effects of Treatment

Prevention Levels of Evidence

1. Evidence obtained from at least one randomized controlled trial
2. Evidence obtained from controlled trials without randomization
3. Evidence obtained from cohort or case-control analytic studies
4. Evidence obtained from multiple-time series with or without intervention
5. Ecologic (descriptive) studies (e.g., international patterns studies, migration studies)
6. Opinions of respected authorities
Prevention Endpoints

A. Cancer Mortality
B. Cancer Incidence
C. Generally accepted intermediate endpoint (e.g., large adenomatous polyps)
Screening Levels of Evidence

1. Evidence obtained from at least one randomized controlled trial
2. Evidence obtained from controlled trials without randomization
3. Evidence obtained from cohort or case-control analytic studies
4. Evidence obtained from multiple-time series with or without intervention
5. Opinions of respected authorities
Treatment Levels of Evidence

1. Randomized controlled clinical trial(s)
   i. Double-blinded
   ii. Nonblinded

2. Nonrandomized controlled clinical trial(s)
   (e.g., allocation by birth date, chart number, etc.)

3. Case series
   i. Population-based consecutive cases
   ii. Consecutive cases (not population-based)
   iii. Nonconsecutive cases
Treatment End Points

A. Total mortality
B. Cause-specific mortality
C. Carefully assessed quality of life
D. Indirect surrogates
   i. Disease-free survival
   ii. Progression-free survival
   iii. Tumor response rate
Selection Bias

Potential Screenees

Screened

Why Did They Come?
Selection Bias in an Ovarian Cancer Screening Program

Design: 5,479 women screened with transabdominal U/S annually x3

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Deaths Expected</th>
<th>Deaths Reported</th>
<th>% Standardized Mortality Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>70</td>
<td>71</td>
<td>101%</td>
</tr>
<tr>
<td>Ovarian</td>
<td>25</td>
<td>22</td>
<td>90% (ns)</td>
</tr>
<tr>
<td>Colorectal</td>
<td>32</td>
<td>19</td>
<td>59%</td>
</tr>
<tr>
<td>Stomach</td>
<td>11</td>
<td>4</td>
<td>45%</td>
</tr>
<tr>
<td>Lung</td>
<td>59</td>
<td>20</td>
<td>34%</td>
</tr>
<tr>
<td>Cervical</td>
<td>9</td>
<td>2</td>
<td>23%</td>
</tr>
<tr>
<td>Other</td>
<td>106</td>
<td>82</td>
<td>77%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>312</strong></td>
<td><strong>220</strong></td>
<td><strong>71%</strong></td>
</tr>
</tbody>
</table>

(Crayford et al., Lancet, 2000)
# Relationship of Placebo Adherence to Mortality

5-Year Mortality in Patients Given Clofibrate or Placebo

<table>
<thead>
<tr>
<th>Adherence</th>
<th>Clofibrate (N=1065)</th>
<th>Placebo (N=2695)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;80%</td>
<td>24.6%</td>
<td>28.2%</td>
</tr>
<tr>
<td></td>
<td><em>p</em>=.0001</td>
<td><em>p</em>=4.7x10^-16</td>
</tr>
<tr>
<td>≥80%</td>
<td>15.0%</td>
<td>15.1%</td>
</tr>
<tr>
<td>Total</td>
<td>18.2%</td>
<td>19.4%</td>
</tr>
</tbody>
</table>

“There is simply no serious scientific alternative to the generation of large-scale randomized evidence.”

R. Peto et al.,
The Hippocratic Injunction

It is worse for a physician to make a patient worse off than it is not to benefit a patient.
OK, Stranger...
What's the circumference of the Earth?.. Who wrote "The Odyssey" and "The Iliad"?.. What's the average rainfall of the Amazon Basin?

Bart, you fool! You can't shoot first and ask questions later!