

Constructing Chains of Evidence

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Constructing Chains of Evidence

Definition:

Chain: series of questions/evidence that, together, describe impact of a (genomic) test.

Issues:

- What questions are in the chain?

In addition to title, IOM assigned 3 topics

1. What is your **model** for data generation or data assessment?
2. Are there any **compromises** in the data which are being generated **relative to RCTs**?
3. What are the **barriers** to making your model a routine evidence generation pathway for genomic tests?

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‘My model’: an established analytic framework.

Established 'Analytic framework'

S. Woolf said (IOM report, 4/10):

- “...roundtable should consider... genomic profiling within... established frameworks for evaluating screening tests. Regardless of the type of test... standard set of analytic principles....” (used by USPSTF, WHO, etc.) including:
- a. accuracy and reliability of test
 - b. effectiveness of early detection (benefit)
 - c. potential harms
 - d. balance of benefit vs harm

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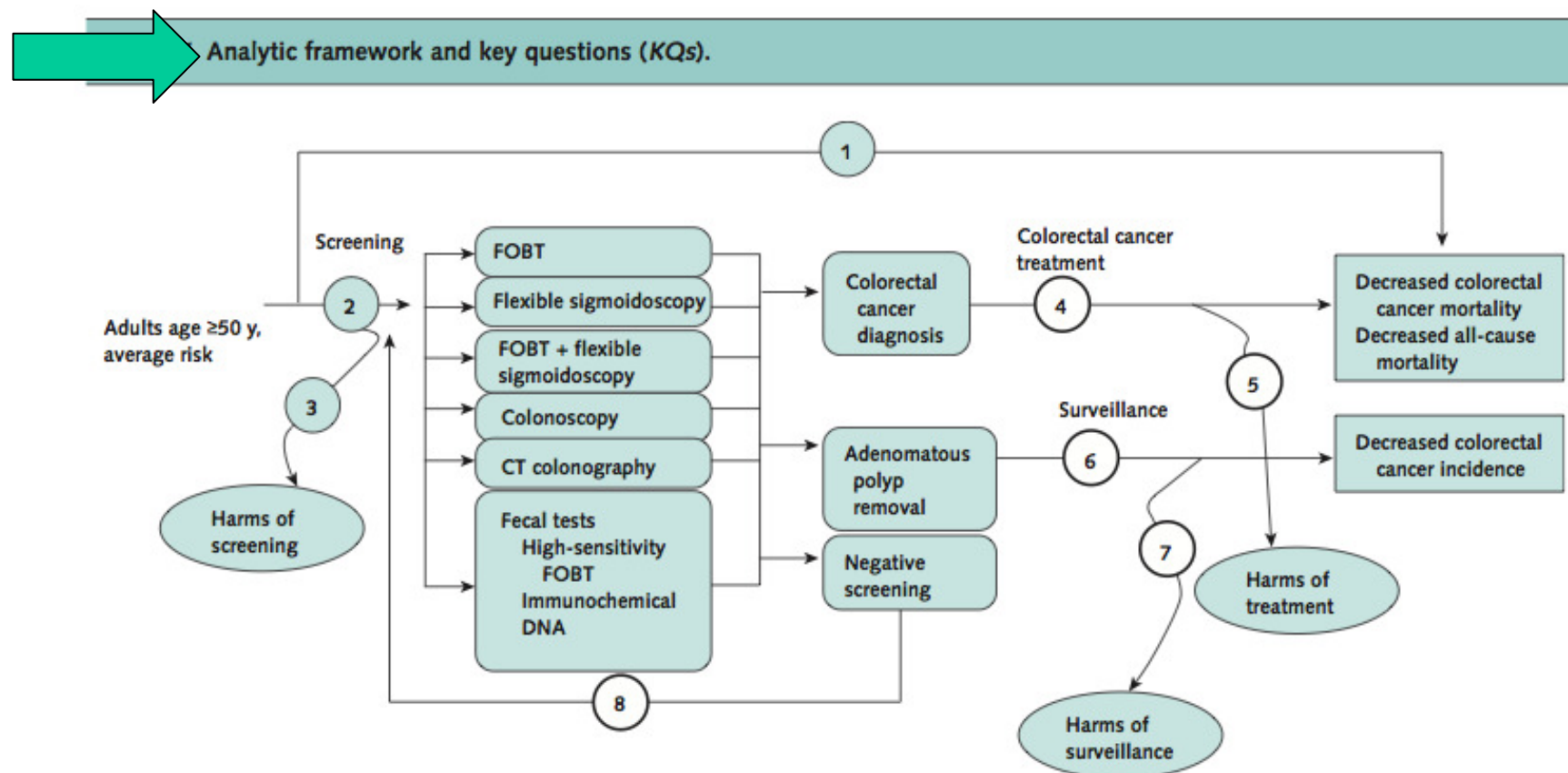
- a. accuracy and reliability of test
- b. effectiveness of early detection (benefit)
- c. potential harms
- d. balance of benefit vs harm

Questions a-d: simple to ask, hard to answer.

RCT, addressing a-d, is 'ideal' source of evidence.

Discussion today, 11 17: Above issues discussed in detail (Piper, Calonge, others); not in 4/10 report.

‘Analytic framework’ (USPSTF; CRC scrng) illustrates ‘key questions’, requiring different pieces of evidence



KQ1: What is the effectiveness of the following screening methods (alone or in combination) in reducing mortality from colorectal cancer? a. Flexible sigmoidoscopy, b. Colonoscopy, c. Computed tomographic (CT) colonography, d. Fecal screening tests: i. High-sensitivity guaiac fecal occult blood test (FOBTs); ii. Fecal immunochemical test; iii. Fecal DNA test.

KQ2a: What are the sensitivity and specificity of 1) colonoscopy and 2) flexible sigmoidoscopy when used to screen for colorectal cancer in the community practice setting?

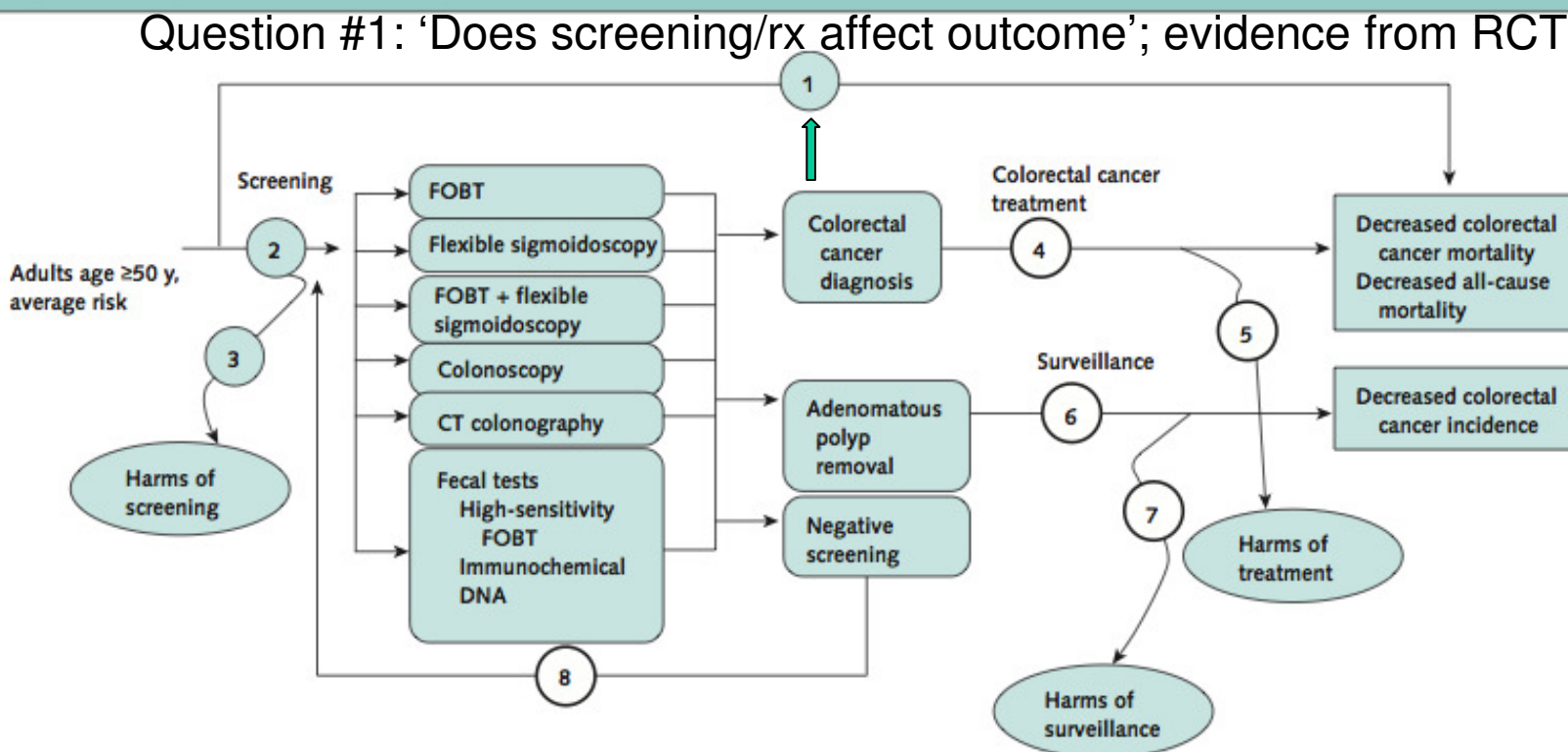
KQ2b: What are the test performance characteristics of 1) CT colonography and 2) fecal screening tests (as listed in KQ1d) for colorectal cancer screening, as compared to an acceptable reference standard?

KQ3a: What are age-specific rates of harm from colonoscopy and flexible sigmoidoscopy in the community practice setting?

KQ3b: What are the adverse effects of newer tests, including 1) CT colonography and 2) fecal screening tests (as listed in KQ1d)?

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Figure 1. Analytic framework and key questions (KQs).



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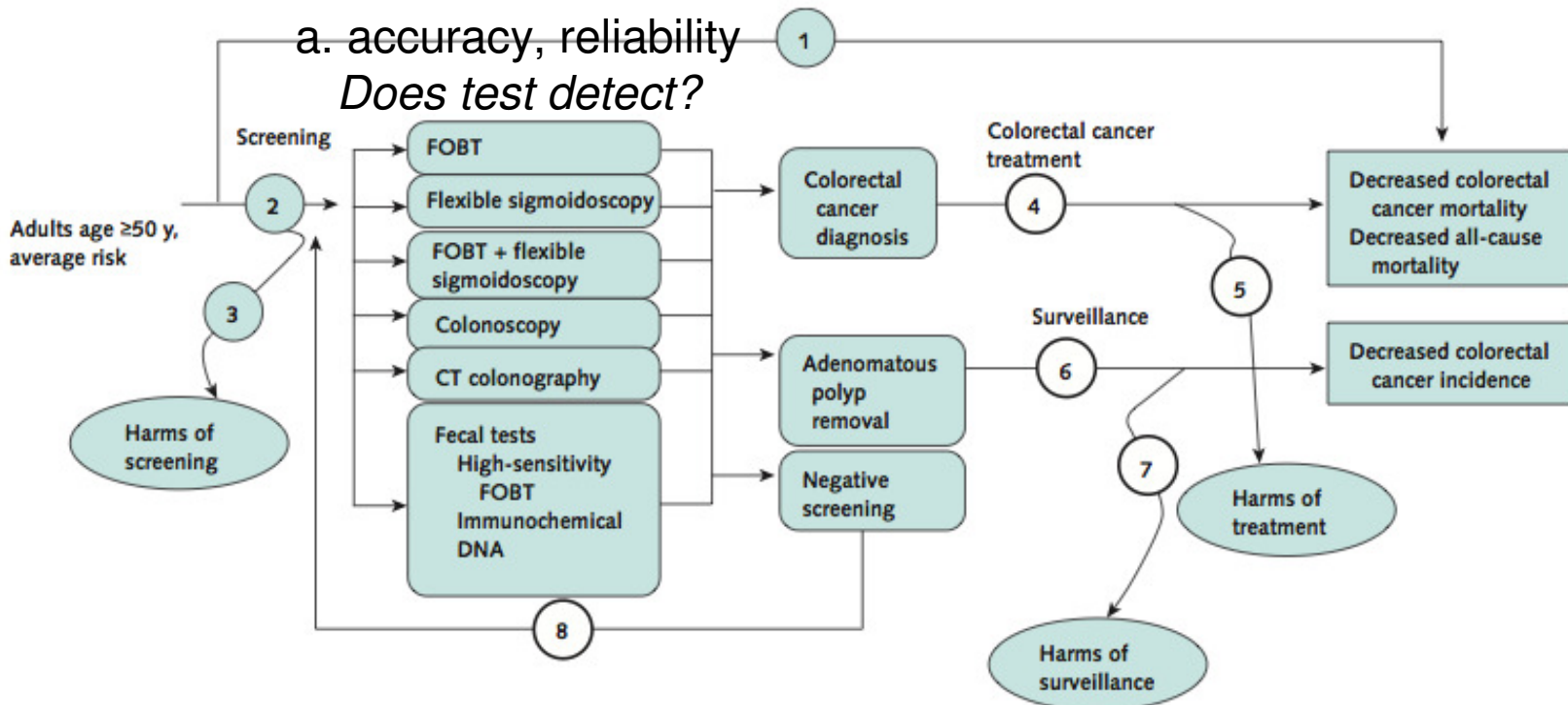
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If no RCT to answer a-d all at once, then 'piece together' a-d

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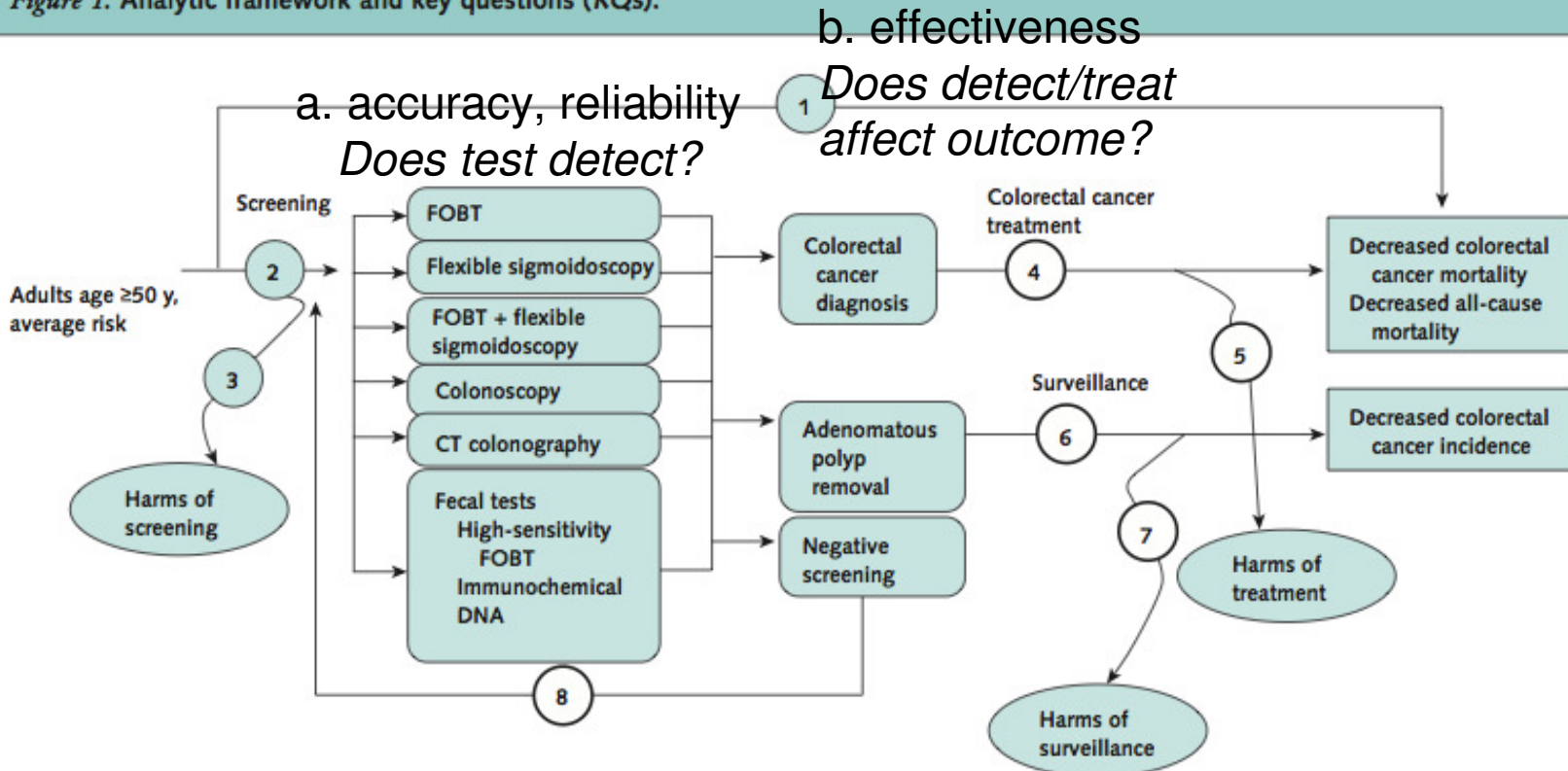
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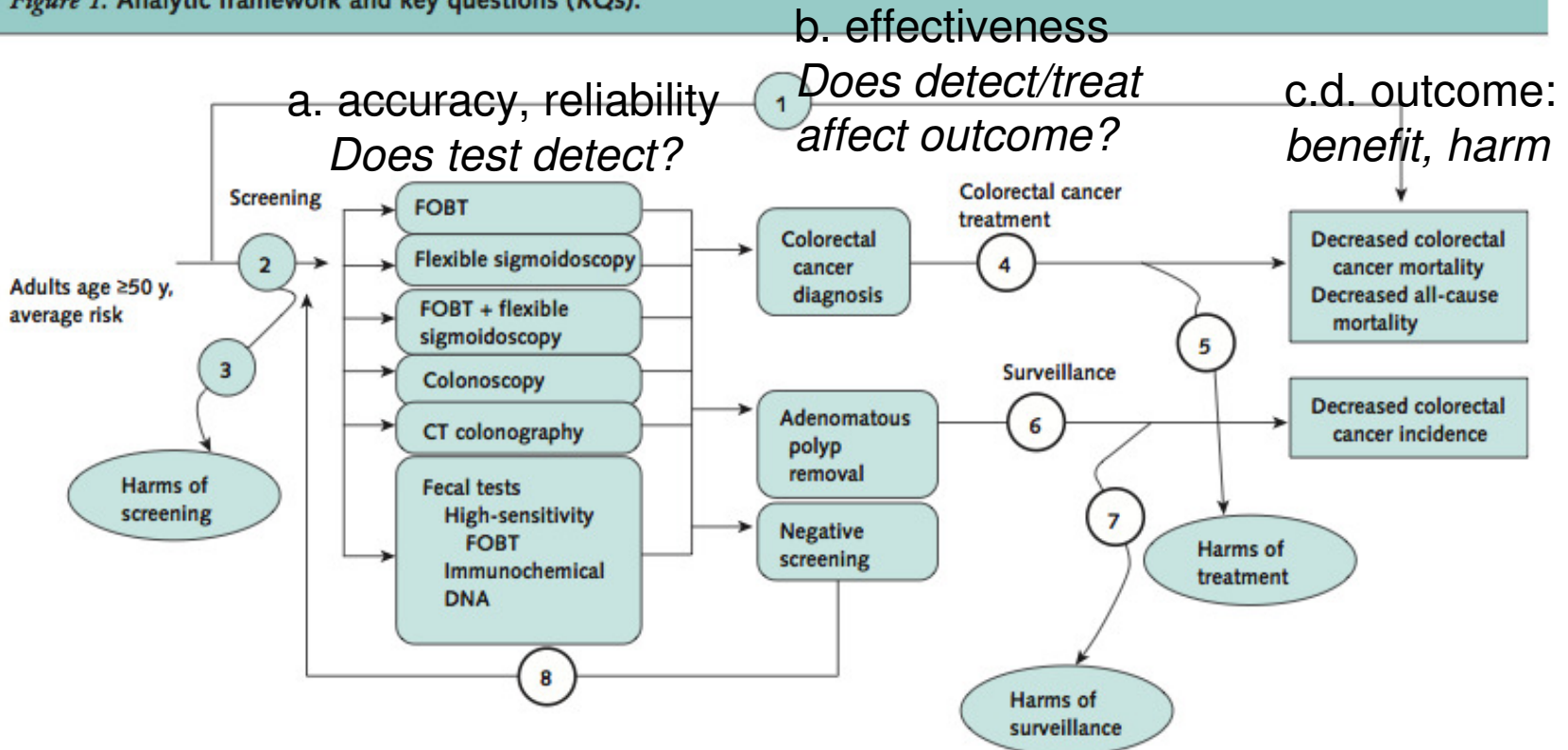
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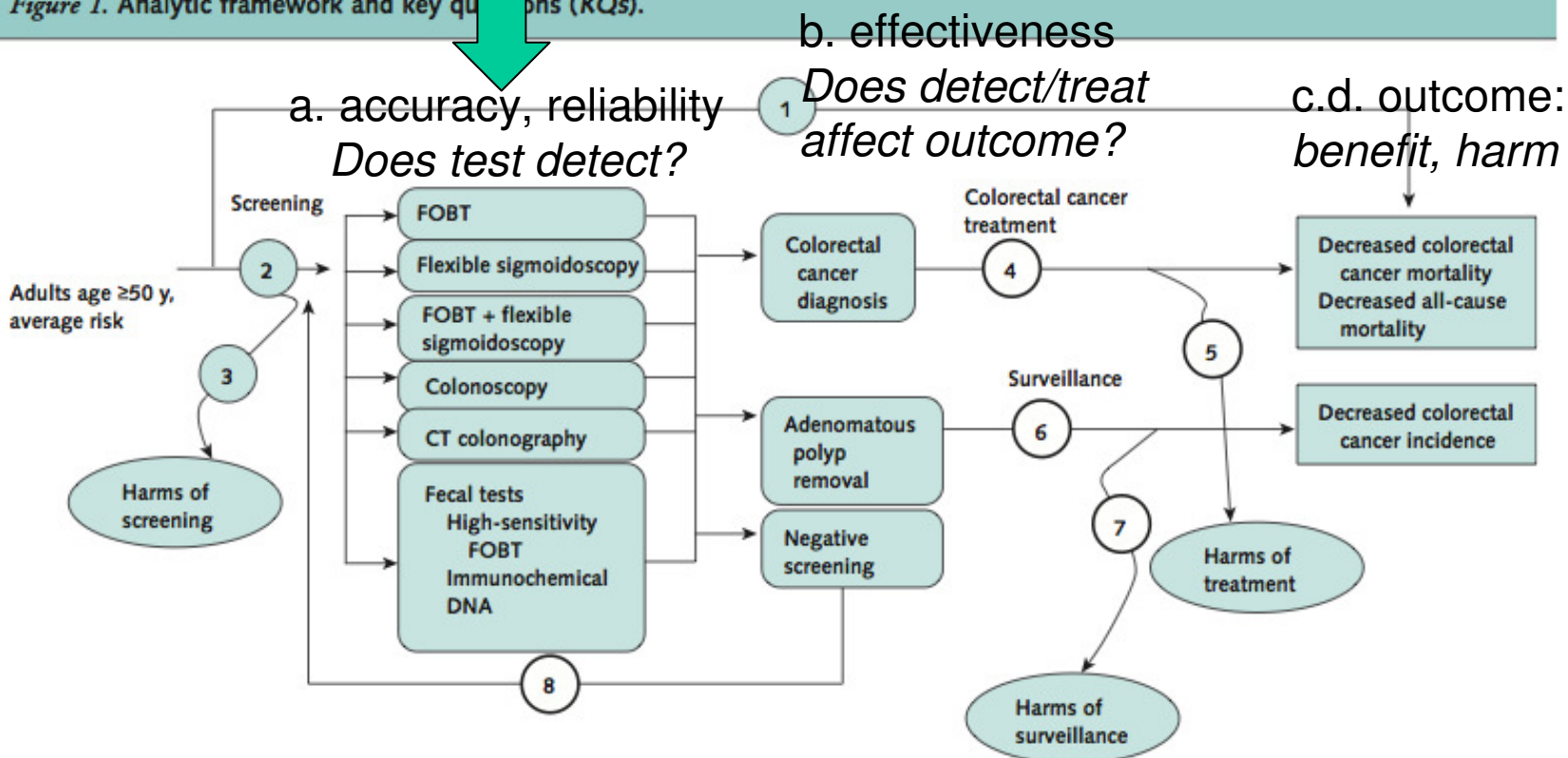
Analytic framework

USPSTF framework, evolved over decades, is basis for clinical decision-making and 'evidence-based medicine' (recently by EGAPP)

- a. accuracy and reliability of test
- b. effectiveness of early detection (benefit)
- c. potential harms
- d. balance of benefit vs harm

Evidence about genomic tests is often limited to (a).

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Lessons from Analytic Framework

Lesson 1: Outcome (benefit/harm) is ‘bottom line’

- *Not sufficient for test to ‘discriminate’ or have biological elegance; **outcome must be improved** by info/action.*

Lesson 2. So research about discovery/development should anticipate outcome, use.

- *For efficient discovery/development, work backwards from a specific clinical decision; benefit, harm; and ‘desired features of test (OncoTypeDx; EXACT)*

OncoTypeDx: can RNA predict BrCa recur

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Multigene Assay to Predict Recurrence of Tamoxifen-Treated, Node-Negative Breast Cancer

Soonmyung Paik, M.D., Steven Shak, M.D., Gong Tang, Ph.D.,
Chungyeul Kim, M.D., Joffre Baker, Ph.D., Maureen Cronin, Ph.D.,
Frederick L. Baehner, M.D., Michael G. Walker, Ph.D., Drew Watson, Ph.D.,
Taesung Park, Ph.D., William Hiller, H.T., Edwin R. Fisher, M.D.,
D. Lawrence Wickerham, M.D., John Bryant, Ph.D.,
and Norman Wolmark, M.D.

NEJM 2004;351:2817

Study Design: evidence from observational cohort;
piggy-backed onto one arm of RCT

Result: a group has good prognosis re recurrence

Comment:

- provides one link in chain (does test discriminate)
- one arm of banked RCT: source of strong evidence
- technological breakthrough: RNA from FFPE
- conceptual breakthrough: work backwards from clinical question/goal

EXACT: can stool DNA diagnose CRC

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Fecal DNA versus Fecal Occult Blood for Colorectal-Cancer Screening in an Average-Risk Population

Thomas F. Imperiale, M.D., David F. Ransohoff, M.D., Steven H. Itzkowitz, M.D.,
Barry A. Turnbull, Ph.D., and Michael E. Ross, M.D.,
for the Colorectal Cancer Study Group*

NEJM 2004;351:2704

Study design: Cross-sectional

Result: DNA test has 51% sensitivity for CRC

Comment:

- 'prospective' study; requires 'unique' stool collection
- provides 'one link in chain' (does test discriminate);
one link may be 'sufficient' if data about other links

Constructing Chains of Evidence

Questions:

1. What is your model for data generation or data assessment? (Ans: 'Analytic framework'.. links in chain)
2. **Are there any compromises in the data which are being generated relative to RCTs?**
3. What are the barriers to making your model a routine evidence generation pathway for genomic tests?

2. Are there any compromises in the data which are being generated relative to RCTs?

1. If no RCT, evidence is necessarily 'limited'
 - e.g. can assess 'discrimination' but *not* 'does discrimination/action affect outcome' (e.g. EXACT)
2. Much 'omic' 'evidence' in 2010 is:
 - re limited question (focus on discrimination)
 - opaque (critical details of design not visible)
 - wrong* ('discrimination' due to bias or error, not biology)

Example:
Bias may explain 'discrimination'

Differential exoprotease activities confer
tumor-specific serum peptidome patterns

Josep Villanueva, David R. Shaffer, John Philip, Carlos A. Chaparro, Hediye Erdjument-Bromage,
Adam B. Olshen, Martin Fleisher, Hans Lilja, Edi Brogi, Jeff Boyd, Marta Sanchez-Carbayo,
Eric C. Holland, Carlos Cordon-Cardo, Howard I. Scher, and Paul Tempst

J Clin Invest 2006;116:271

Results: Peptide patterns are ~100% sensitive, specific for prostate cancer.

Why pick proteomics problem?

*Answer: Issues similar in many 'omics' fields; but is well-documented here.
(Research design/conduct is opaque in many journals, especially basic).*

Bias may explain 'discrimination'

Compared groups are different:

- Cancer: mean age 67 y.o.; 100% men

Bias may explain 'discrimination'

Compared groups are different:

- Cancer: mean age 67 y.o.; 100% men
- Control: mean age 35 y.o.; 58% women

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- Cancer: mean age 67 y.o.; 100% men
- Control: mean age 35 y.o.; 58% women

Comment:

This study reported detail; but if 'omics' studies are opaque, cannot assess 'strength'.

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- a. If 'analytic framework' model is a 'pathway':
 - good news: makes (clinical) sense; experience (USPSTF)
 - bad news (barrier): not easy to get evidence
- b. One barrier in 'thinking': investigators may not think of **data as *product of a study***.. If study design is weak, then so is 'link'. ('Design as carefully as if 'prospective': Hayes)
- c. Rate-limiting step:
 - is *not* funding, infrastructure, informatics, sharing data
 - is* formulating clinical question(s) and then designing study that provides strong evidence/link
- d. Question: Can 'existing data' be used in strong design?

Example: **prognosis** study design 'superimposed' on practice data

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Five-Year Risk of Colorectal Neoplasia after Negative Screening Colonoscopy

Thomas F. Imperiale, M.D., Elizabeth A. Glowinski, R.N., Ching Lin-Cooper, B.S.,
Gregory N. Larkin, M.D., James D. Rogge, M.D., and David F. Ransohoff, M.D.

NEJM 2008;359:1218

Question: Prognosis: ability to predict future CRC

Result: Very low risk of CRC at 5yr

Study design: Observational cohort (assess prognosis)

Comment:

- 'study' superimposed on practice (Lilly); opportunistic
- an 'omic' marker, if available, could have been studied

Example: **diagnosis** study design 'superimposed' on practice data

RISK OF ADVANCED PROXIMAL NEOPLASMS IN ADULTS ACCORDING TO THE DISTAL COLORECTAL FINDINGS

RISK OF ADVANCED PROXIMAL NEOPLASMS IN ASYMPTOMATIC ADULTS ACCORDING TO THE DISTAL COLORECTAL FINDINGS

THOMAS F. IMPERIALE, M.D., DAVID R. WAGNER, M.S., CHING Y. LIN, B.S., GREGORY N. LARKIN, M.D.,
JAMES D. ROGGE, M.D., AND DAVID F. RANSOHOFF, M.D.

NEJM 2000;343:169

Question: Diagnosis: can colonoscopy detect CRC

Result: 'Yield' of screening in asymptomatic persons

Study design: Cross-sectional

Comment:

- 'study' superimposed on practice; opportunistic
- an 'omic' marker, if available, could have been studied

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 - Suggestions for future

Suggestions for future

1. Understand that 'analytic framework' (to assess impact of a test on outcome) provides an established method to assess clinical and policy decisions. (USPSTF, EGAPP)
2. In this conceptualization, genetic/genomic information is not 'exceptional'.

Good news: method/framework available

Bad news: not 'easy'; has same problems as all questions of prognosis, prediction/response-to-rx.

Suggestions for future

3. Sources of data/evidence when 'ideal' RCT (assess impact of test on outcome) are not available:
 - banked RCTs may answer 'part' of the question
 - e.g., about prognosis, prediction, side-effects; ?**diagnosis**
 - other sources may be useful; be opportunistic
 - e.g., HMOs: cohort data; experience in design (K-P, GH)
4. Main issue: not data analysis/sharing etc; rather it's 'What ***study design*** is needed to answer what ***specific question***'; then find/get data (and 'do as rigorously as if 'prospective study.'')

Suggestions for future

5. Suggested overall approach:

- *Do not* overly focus on infrastructure, informatics, data sharing (what 4.10 report suggested), etc.
- *Do* focus on answering specific questions, opportunistically (in 'easy' settings, when possible).
 - Learn how to design strong research study (e.g. OncoTypeDx; other) in different settings; then scale up.
 - what other sources besides RCTs
 - what about problems besides progn/predic.

end