Observational data – a critical platform for Comparative Effectiveness Research

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In 2009, the Institute of Medicine’s Roundtable on Evidence-Based Medicine identified two major challenges:

- Many doctors don’t have evidence available when needed for clinical decision-making
- Evidence is not applied for effectiveness and efficiency

Opportunity:

We need a new clinical research paradigm—we need “learning health care systems”
Why is evidence so hard to find?

The more we screen, the more we’ll find – let’s screen everyone

“Getting a mammogram saved my life”

…First do no harm…
Example 1: should we screen for prostate cancer?
Example 2: Screening for lipid disorders in children and adolescents

Key Questions
1. Is screening for dyslipidemia in children/adolescents effective in delaying the onset and reducing the incidence of CHD-related events?
2. What is the accuracy of screening for dyslipidemia in identifying children/adolescents at increased risk of CHD-related events?
2a. What are abnormal lipid values in children/adolescents?
2b. What are appropriate tests? How well do screening tests (non-fasting total cholesterol, fasting total cholesterol, fasting lipoprotein analysis) identify individuals with dyslipidemia?
2c. How well do lipid levels track from childhood to adulthood?
2d. What is the accuracy of family history in determining risk?
2e. What are other important risk factors?
2f. What are effective screening strategies for children/adolescents (including frequency of testing, optimal age for testing)?
3. What are the adverse effects of screening (including false positives, false negatives, labeling)?
4. In children/adolescents, what is the effectiveness of drug, diet, exercise, and combination therapy in reducing the incidence of adult dyslipidemia, and delaying the onset and reducing the incidence of CHD-related events (including optimal age for initiation of treatment)?
5. What is the effectiveness of drug, diet, exercise or combination therapy for treating dyslipidemia in children/adolescents?
6. What are the adverse effects of drug, diet, exercise, and combination therapy in children/adolescents?
7. Does improving dyslipidemia in childhood reduce the risk of dyslipidemia in adulthood?
8. What are the cost issues involved in screening for dyslipidemia in children/adolescents?
Why is CER possible with observational data

- Large populations in real world settings
  - Ability to examine community practice vs. academic centers
  - Variety of patients and providers
    - When outside trial settings → more generalizable individuals
  - Geographic diversity
- Access to health care
Why are observational data **essential** for CER?

- **Relevancy**
  - Effectiveness over efficacy

- **Timeliness**
  - RCTs impractical for timely evidence

- **Impact on priority populations & subpopulations**
  - Large samples with ability to study subgroups
    - Many of these populations are excluded from efficacy studies
  - Able to capture unbiased estimates of harm/benefits at various points
Observational data opportunities and research platforms

- Group Health Cooperative
- Breast Cancer Surveillance Consortium
- HMO Research Network
  - Cancer Research Network (CRN)
  - Collaboratory
Breast Cancer Surveillance Consortium

- **Academic settings**

- **Identified community-based radiology facilities within a defined area with access to:**
  - Cancer registries
  - Pathology databases

- **Primary data collection**

- **Many data elements (mammography findings, cancer) are mandated by law**

- **Statistical Coordinating Center**
  - Each site submits data in data dictionary form annually
Core Pooled BCSC Data

Figure 1: Cancer care continuum and BCSC data resources

**PROCESS SURVEILLANCE**

- **Patient Factors**
  - Age
  - Screening history
  - Family history
  - Menopause status
  - Hormone therapy
  - BMI
  - Race/ethnicity
  - Breast density
  - Comorbidity

- **Screening Examinations**
  - Film-screen mammography
  - Digital mammography
  - Ultrasound

- **Diagnostic Evaluations**
  - Film-screen mammography
  - Digital mammography
  - Ultrasound
  - **Breast MRI**
  - Fine needle aspiration
  - Core biopsy
  - Surgical biopsy

**OUTCOME SURVEILLANCE**

- **Intermediate Outcome**
  - Cancer detection rate
  - Interval cancer rate
  - Cancer stage
  - Tumor size
  - Tumor markers

- **Treatment**
  - Mastectomy
  - Breast conserving surgery
  - Radiation
  - Adjuvant chemotherapy

- **Long-term Outcome**
  - Breast cancer mortality reduction
  - All-cause mortality reduction

**Radiology Information**

- Radiologist Information
- Facility Information

**Pathology (malignant and benign)**

**Cancer**

**Vital Status**

Medicare Claims Data, Women Age 65+, 1998-2006
- Comorbidity
- Mammography
- Ultrasound
- MRI
- Biopsy
- Treatment

2.1 million women & 55,000 breast cancers
Breast Cancer Surveillance Consortium

- Risk factors and outcomes from
  - Total mammograms = 8,374,024
  - Total women = 2,153,296
  - Screening mammograms = 5,981,957
  - Diagnostic mammograms = 1,137,648
  - Ultrasounds = 569,615

- Breast cancers
  - Invasive cancers = 65,313
  - In situ cancers = 13,263
Observational International comparisons

Different screening strategies in the US vs. other countries – what can we learn about how practice influences outcomes?
Recall is lower at same cancer detection rate in the UK vs. US

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Recall</th>
<th>Cancer detection rate</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>UK</td>
<td>BCSC</td>
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<tr>
<td></td>
<td>U.K.</td>
<td>BCSC</td>
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<tr>
<td>50-54</td>
<td>7.6</td>
<td>14.6</td>
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<td>55-59</td>
<td>7</td>
<td>13.7</td>
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<tr>
<td>60-64</td>
<td>6.7</td>
<td>12.6</td>
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*UK performs far fewer diagnostic tests and open surgical biopsies to diagnose same number of cancers*

Smith-Bindman et al *JAMA* 2003
Norway vs. US

- Interval cancer rates are significantly lower in Norway than in North Carolina

- Interval cancer rates higher in Vermont
  - But - diagnosed tumors tended to be at an earlier stage than those diagnosed in the Norwegian women
  Hofvind *JNCI* 2008
Observational studies that extend evidence from RCTs
Breast cancer screening

- 15-30% mortality reduction from breast cancer screening
  - Trials done long time ago
    - Different technology, ages and intervals, better understanding of harms
  - How do we generate evidence to inform outstanding questions?
- Burning questions:
  - Screening frequency
  - Ages to screen
  - Should frequency differ with age?
Late stage breast cancers are no more likely for women on a 2 year screening intervals vs. 1 year, except for younger women. These findings are useful for policy decisions about appropriate screening intervals and for use in statistical models that estimate the costs and benefits of mammography by age and screening interval.
Mammography does not work as well in younger women

- **12 months**
  - 68% of missed cancers explained by higher mammographic breast density in younger women

- **24 months**
  - 31% of missed cancers because of faster growing tumors
  - 38% because of higher breast density

→ These findings were just supported by large modeling effort by one of the CISNET modeling groups
CER studies to test ways of improving screening

- Outreach
- Screening strategy
- Changing risk factors
- New technology
Reminding women to schedule a mammogram is as efficacious as addressing barriers.

Simple intervention groups need to be included as comparison groups in randomized trials so that we better understand more complex intervention effects.
Clinical breast exam had modest incremental benefit to invasive cancer detection over mammography alone, but results in more false-positive results.
Other examples from: BCSC-GO grant

Optimal screening intervals based on risk factors

Downstream healthcare use and costs for film vs. digital screening

Comparative effectiveness and cost effectiveness of different screening strategies for different screening intervals & start/stop ages

→ Much more data that can be used for CER to inform evidence gaps
Group Health Cooperative &
Group Health Research Institute (GHRI)
What Is Group Health Cooperative?

- Mixed model HMO
- Consumer governance
- ~620,000 enrollees in Washington State
  - ~350K in integrated group practice
- GHC’s mission is to “transform health care”
Why is CER possible?

- Defined, accessible enrollee population
- Defined, accessible provider population
- High quality, clinically relevant automated data (current and historical) that is organized for research application
Unique Data Resources & Research Capabilities

**Automated data files**
- Ambulatory Care with Dx
- Pharmacy
- Inpatient
- Radiology
- Laboratory
- Pathology
- Costs of care
- Disease registries
- Immunization registry
- Breast cancer screening registry
- Electronic Medical Record

**Research Capabilities**
- Survey Research Program
- Research Clinic
- Medical Records Abstraction
- Data Management
- Records Linkage Studies
- “Real-world” intervention trials
- Multi-Center Studies
- HMO Research Network
- Ethical Conduct of Research

Virtual Data Warehouse (VDW)

The VDW is populated by automated data from the following sources:

- Tumor registry
- Enrollment
- Demographics
- Pharmacy
- Utilization
- Geocoding
- Laboratory
- Chemotherapy
- Radiology
- Pathology
A learning health care system

- Research happens closer to clinical practice than in traditional university settings
- Scientists and clinicians work together
- Studies occur in everyday practice settings
- Electronic medical records are linked and mined for research
- We recognize that clinical data exist for the public good
Collaboration is critical

- Partnerships with academic medical centers
- Major universities (UW, Harvard, UCSF, etc.)
- Connects academic medical research to our community
- Founding leader of the HMO Research Network
  - 15 health plans nationwide
  - Multi-site studies add statistical power and diversity to our research
GHRI Focal Areas

- Biostatistics
- Cancer Prevention & Control
- Chronic Illness Care
- Patient-centered Care
- Immunization
- Improved health & health care through research, innovation & dissemination

- Women’s Health
- Health Systems Organization & Finance
- Preventive Care & Health Promotion
- Medication Safety & Effectiveness
- Behavioral Medicine & Mental Health
Research on bicycle safety

- 1989 case-control study with Harborview Injury Prevention and Research Center: Bike helmets reduce the risk of head injuries by 85% and brain injuries by 88%.

- 1994 study: A Group Health/Harborview bicycle helmet campaign proves cost effective, increases the use of helmets, and reduces admission rates for head injuries.

- From 1992 to 1997: A 67% decrease in the rate of ER-treated bicycle head injuries in Group Health kids ages 5 to 14 associated with an increase in helmet use from 4% to 48%.

→ These findings have accelerated the use of bike helmets nationwide.
Research on low back pain

• 2001: Massage works well for low back pain—better than self-care and acupuncture. (Massage patients used fewest medications and had the lowest costs of subsequent back care.)

• 2005: Yoga is more effective for back pain than conventional exercise (aerobics, strengthening, stretching).

• 2009: Acupuncture eases back pain better than usual care. (But skin penetration may not be key.)

→ Though it’s not clear why these modalities work, patient are finding relief with non-invasive, relatively inexpensive approaches.
Research on healthy aging

• 2005: Seniors who exercise three or more times a week have a 30 to 40% percent lower risk for developing dementia compared with those who exercise less.

• 2006: Good physical function is linked to delay in Alzheimer’s disease, suggesting that re-engaging in physical activity may help to stop or slow cognitive decline.

• 2008: Seniors who participate in Group Health’s fitness programs have lower health care costs.

Based on these findings, we can advise elderly patients to “use it even after you start to lose it.”
Why are these CER results important?

- Impact tens of millions of lives
- Discovered by studying a large, stable, real-world population: the Group Health membership
- Provide answers that Group Health patients can use today to live healthy, active lives
- Provide evidence that doctors can use in their practices every day

→ could not have been done as prospective RCTs
Hallmarks of HMORN Sites

- Research centers embedded in integrated delivery systems
  - Delivery systems provide both care and coverage
  - Access to a defined population of members
  - Comprehensive electronic data facilitate longitudinal evaluation of care practices and associated clinical outcomes
- Research centers are highly interdisciplinary—instills a “culture of collaboration” across sites
- Long-standing partnerships with academic institutions
- Strive for “bidirectional learning” between our research centers and health care delivery systems
- Similar enough to partner, different enough to ensure diversity and heterogeneity in our patient populations, patterns of care, delivery system design
National Cancer Institute funded Cancer Research Network
Cancer Research Network Sites

Group Health, Group Health Research Institute
Kaiser Permanente Northwest, Center for Health Research/Northwest
Kaiser Permanente Northern California, Division of Research
Kaiser Permanente Southern California, Department of Research and Evaluation
Kaiser Permanente Hawaii, Center for Health Research/Hawaii
HealthPartners, HealthPartners Research Foundation
Marshfield Clinic, Marshfield Clinic Research Foundation
Kaiser Permanente Colorado, Institute for Health Research
Lovelace Health Plan, Lovelace Clinic Foundation
Health Alliance Plan, Henry Ford Health System
Harvard Pilgrim Health Care Institute, Department of Population Medicine
Fallon Community Health Plan, Meyers Primary Care Institute
Geisinger Health Plan, Center for Health Research
Kaiser Permanente Georgia, Center for Health Research/Southeast
Cancer Research Network

- Goal: to increase delivery of effective preventive, curative & supportive interventions for major cancers and rare tumors.
- Research portfolio covers full spectrum of cancer control, with studies on prevention, early detection, treatment, survivorship, surveillance, and end-of-life care.
- Key features of the CRN’s population laboratory:
  - >11 million enrollees across 14 sites
  - Racial/ethnic and geographic diversity
  - Large number of rare cancers
  - High retention of enrollees
Center for Cancer Screening CER set in CRN.

Range of expertise and experience among investigators

Addresses evidence gaps on effectiveness of CRC and Cervical Cancer screening tests

- Evidence synthesis

- Create new evidence and methods
1. Assembling national data sets (CRN, SEER-Medicare, Medicaid, and NCCN) to support studies of patterns of care and outcomes.

2. Develop, validate, and implement strategies to enhance the accuracy of key data elements.

Legend:
- SEER-Medicare
- Registry-Medicaid
- CRN Site
- NCCN Center
Examples of Large Collaborative Studies

- Cancer Research Network (11 health plans)
  - Cancer epidemiology, prevention, early detection and control
  - Includes 3.5 percent of U.S. population

- Breast Cancer Surveillance Consortium
  - Represents 5% of the US population

- Centers for Education and Research on Therapeutics (CERT - 10 health plans)
  - Studies in drugs and patient safety
  - Includes 2-3 percent of U.S. residents

- Vaccine Safety Data Link (8 health plans)
  - Includes 2 percent of all children nationwide
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- Impact on priority populations & subpopulations
  - Large samples with ability to study subgroups
    - Many of these populations are excluded from efficacy studies

- Able to capture unbiased estimates of harm/benefits at various points

→ critical to have strong methodology
Conducting CER within clinical systems is possible, but worth remembering…

- Takes time and funding to engage with clinics and clinicians
  - Integrating with the clinical flow
- Need to be clear on where research ends and clinical care begins
- Getting realistic budget estimates and TIME! for interactively working with clinical systems
- Clinical priorities are often not aligned with research priorities – particularly true for timelines
For further information about GHRI

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For further information about the BCSC

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More information see our web site:
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For further information about the CRN

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More information see our web site:

www.crn.cancer.gov