Generating evidence-about effectiveness and value

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Member GIN, LMIC Committee Member

"Everything should be made as simple as possible but not simpler.”

……………...(Albert Einstein)

The Future: Personalized Healthcare
Clinical Certainty & Efficiency

Acquisition
Integration

Personalization

Diagnostic Complexity
Sophisticated Decision Support

Evidence-Based Medicine & Patient-Centered Choice

A. Good evidence/ Important to patient
B. Good evidence
C. Potential for good evidence
D. Important to patient choice/potential for good evidence
E. Important to patient choice/ No potential for evidence

Hierarchy of evidence

STUDY DESIGN
- Randomized Controlled Trials
- Cohort Studies and Case Control Studies
- Case Reports and Case Series, Non-systematic observations

BIAS

BEST
EVIDENCE

Expert Opinion

Darius Lakdawalla et al. Health Aff 2015;34:555-561
©2015 by Project HOPE - The People-to-People Health Foundation, Inc.

Trends In Cost Of A Twenty-Four-Week Colorectal Cancer Treatment Regimen And Change In Quality-Adjusted Cost Of Care For Colorectal Cancer, 1999–2005.

Data from reference: Health Affairs 2015;34:555-561
The best evidence

**Eminence based medicine**

- **Eloquence based medicine**

- **Emotion based medicine**

**Evidence Based Medicine**

(old school)

**Evidence Based Medicine**

(1. addresses health outcomes and not just intermediate outcomes
2. is from “real” patients
3. considers harms and benefits
4. fits the circumstances
5. comes from well-designed, well conducted studies

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**The EBM Triad**

![Diagram of the EBM Triad](image)

- **Evidence-based clinical decisions**
  - Clinical state and circumstances
  - Individual Clinical Expertise
  - Best External Evidence

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**Some limitations of evidence based medicine**

Many questions do not have answers!

- Evidence from populations - ?Relevance to individual
- Trials - not ‘real’ usage
- Lack of local ownership of recommendations

**Clinical effectiveness vs cost effectiveness**

- Patients with multiple chronic conditions
  - Those to whom most guidelines could apply, yet no guidelines ‘made’ for them
  - To enable stratified guidelines
  - Need to generate science
  - Ensure reporting and packaging off information
  - Perhaps prioritize clusters off conditions

- Encourage guideline developers to take steps in this direction

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**Clinical Practice Guidelines (CPGs) and People with Multimorbidity**

Prevalence of co-occurring chronic conditions is high

- CPGs developed for and emphasize single disease perspective

"Treating an Illness Is One Thing. What About a Patient With Many?"

New York Times, March 31, 2009

Image: Brendan Smialowski for the New York Times

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**Evidence-based Practice and Healthcare**

**Seven Steps**

<table>
<thead>
<tr>
<th>Step</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Cultivate a spirit of inquiry</td>
</tr>
<tr>
<td>1</td>
<td>Ask clinical question in PICOT format</td>
</tr>
<tr>
<td>2</td>
<td>Search for the best evidence</td>
</tr>
<tr>
<td>3</td>
<td>Critically appraise the evidence</td>
</tr>
<tr>
<td>4</td>
<td>Integrate the evidence with clinical expertise and patient preferences and values</td>
</tr>
<tr>
<td>5</td>
<td>Evaluate the outcomes of the practice decisions or changes based on evidence</td>
</tr>
<tr>
<td>6</td>
<td>Disseminate the result</td>
</tr>
</tbody>
</table>

**Other models in use**

- **Population, Interest (area of)**
- **Comparison intervention or group, Outcome, Time**

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**Reassessment of clinical practice guidelines**

Editorial by Shaneyfelt and Centor (JAMA 2009)-

"Too many current guidelines have become marketing and opinion-based pieces…"

"AHA CPG: 48% of recommendations are based on level C – expert opinion…"

"…clinicians do not use CPG […] greater concern […] some CPG are turned into performance measures…”

"Time has come for CPG development to again be centralized, e.g., AHQR…"
Where GRADE fits in

Prioritize problems, establish panel
Systematic review
Searches, selection of studies, data collection and analysis
Assess the relative importance of outcomes
Prepare evidence profile
Quality of evidence for each outcome and summary of findings
Assess overall quality of evidence
Decide direction and strength of recommendation
Draft guideline
Consult with stakeholders and/ or external peer reviewer
Disseminate guideline
Implement the guideline and evaluate

GRADE
Systematic review
Guideline development
PICO
Outcome Outcome Outcome Outcome
Critical Important Critical Not

Summary of findings & estimate of effect for each outcome
Rate overall quality of evidence across outcomes based on lowest quality of critical outcomes

RCT Start high, Obs. data start low
1. Risk of bias
2. Inconsistency
3. Indirectness
4. Imprecision
5. Publication bias
Grade down
Grade up
1. Large effect
2. Dose response
3. Confounders
Very low Low Moderate High

Formulate recommendations:
• For or against (direction)
• Strong or weak (strength)
By considering:
/boxshadowdown
Quality of evidence
/boxshadowdown
Balance benefits/harms
/boxshadowdown
Values and preferences
Revise if necessary by considering:
/boxshadowdown
Resource use (cost)
• “We recommend using…”
• “We suggest using…”
• “We recommend against using…”
• “We suggest against using…”

Practical Clinical Trials
1. Compare clinically relevant interventions
2. Enroll a diverse study population
3. Recruit from a variety of practice settings
4. Measure a broad range of relevant health outcomes

PCTs vs. ECTs

Practical Clinical Trials
Explanatory Clinical Trials

Hypothesis and study design are formulated based on information needed to make a decision
Designed to better understand how and why an intervention works

Addresses risks, benefits, and costs of an intervention as they would occur in routine clinical practice
Maximize the chance that biological effect of a new treatment will be revealed by the study

Models of Research

Traditional Model
Patient-Centered Model (PCORI)

<table>
<thead>
<tr>
<th>Audience</th>
<th>Other researchers, make policy makers.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Products</td>
<td>Presentations at scientific meetings, journals</td>
</tr>
<tr>
<td>Patient Involvement</td>
<td>only data collection and analysis</td>
</tr>
<tr>
<td>Stakeholder Involvement</td>
<td>only data collection and analysis</td>
</tr>
</tbody>
</table>

Patient-Centered Model

<table>
<thead>
<tr>
<th>Audience</th>
<th>Investigators, health care professionals, organizations, policy makers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Products</td>
<td>Research articles, presentations, guidelines, public policy briefs</td>
</tr>
<tr>
<td>Patient Involvement</td>
<td>Involved in determining the acceptability of an intervention</td>
</tr>
<tr>
<td>Stakeholder Involvement</td>
<td>Involved in determining the acceptability of an intervention</td>
</tr>
</tbody>
</table>

*Reported in a manner understandable to each target audience.

Mechanisms that allow patients to collect outcomes from home before or after an office visit have proved helpful. Improving patient engagement continues to be seen as a necessary step for improving the efficiency and safety of care. — Health Affairs 35, no.4 (2016):575-582

Efficacy Standards - IOM

Post 1960
➤ Evidence of Effectiveness
1. Defined as benefit to patients, not to doctors or to society at large
2. Safety to the patient

Clinical benefit
a) Survival extension
b) Improvement in function
c) Quality of Life

Cost Effectiveness – Never Considered
1. Patient reported outcomes are UNEQUIVOCAL. Patient reported outcomes are difficult to blind, serial assessments are required.

2. Soft end points:
- Objective response rates
- Time to progression
- Progression free survival
- Disease free survival

3. Clinical significance to changes in quality of life is unclear.

4. Combined tumor effects and quality of life are more tangible and credible.


What constitutes reasonable evidence of efficacy and effectiveness in cancer?

1. Evidence – that which tends to prove or disprove something, ground of belief or proof.
2. Criteria for evidence in absolute certainty, is difficult.
3. P-value is statistical.
4. Clinical trials are not perfect.
5. Evidence is often unavailable, inconclusive or contradictory.

Randomized clinical trials are considered as Gold Standards

- Not everything can be randomized.
- Other forms of analysis such as propensity score, statistical modelling may facilitate casual inference.
- Co-variates do not determine whether the patient do well or bad.

Clinical components of Randomized trials

1. Designation of pre-specified hypothesis with primary, and secondary end points.
2. Pre specified data cut-off for any continuous measurement to define what constitutes a positive or negative finding.
3. Define sample sets with eligibility criteria that are as inconclusive as possible.

1. Power calculation to show that there is a reasonable probability of definitely answering the research question.
2. Un-bias – ascertainment of end points including blinding wherever possible and ethical protocol specified criteria and independent review of end points.
3. Complete information through a standard follow up schedule and a few patients lost to follow up.
1. After being efficacious in RCTs, treatment are often refined to be studied in community where control environment is lost
2. Doses and schedules are changed
3. Combination are made
4. Drugs are often used off label

TWO SOLUTIONS
a) Cluster Randomization
b) Large simple pragmatic trials - QASAR
c) Evidence can be evaluated on a hierarchy of end point strength – eg Overall Survival
d) Use of biomarkers

Evidence based medicine (1)
Potential questions
- Is the clinical trial population representative of real-life?
- Cost-effectiveness over established (generic) comparator
- What do we know about the risk of polymedication?
- Will frail patients have the same benefit/risk profile?
- Costs and benefits for individual and society?

Challenges
- Balancing risk of involving frail/older patient in clinical trials
- Creating an "orphan" older population? (not authorising/not reimbursing)
- Design appropriate pharmacovigilance for unknowns
- Communicating to reduce inappropriate prescription

Evidence based medicine (2)
Assessment report: geriatric tables

<table>
<thead>
<tr>
<th>Potential areas</th>
<th>Elderly population</th>
<th>Other population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy and Safety Studies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Human PK Studies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Human PD Studies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biopharmaceutical Studies</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>AE leading to drop-out</th>
<th>Psychiatric disorders</th>
<th>Nervous system disorders</th>
<th>Accidents and injuries</th>
<th>Cardiac disorders</th>
<th>Vascular disorders</th>
<th>Cerebrovascular disorders</th>
<th>Infections and infestations</th>
<th>Quality of life decreased</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Fatal</td>
<td>- Hospitalization/prolong existing hospitalization</td>
<td>- Life-threatening</td>
<td>- Disability/incapacity</td>
<td>- Other (medically significant)</td>
<td></td>
<td></td>
<td></td>
<td>Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures</td>
</tr>
</tbody>
</table>
CER Concept and Definitions

Comparative Effectiveness Research (CER) is the generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, or manage a clinical condition or to improve the delivery of care. The purpose of CER is to inform health care decisions, whether by patients, providers, payers, or policy makers, by comparing different options and evaluating their relative merits or outcomes.

Other definitions offer considerable overlap. The American College of Physicians defines CER as the evaluation of the relative (clinical) effectiveness, safety, and cost of two or more medical services, drugs, devices, therapies, or procedures used to treat the same condition. The Institute of Medicine (IOM) – Roundtable on Evidence-Based Medicine defines CER as the comparison of one diagnostic or treatment option to ≥1 others. Primary CER involves the direct generation of clinical info on the relative merits or outcomes of one intervention in comparison to ≥1 others. Secondary CER involves the synthesis of primary studies to allow conclusions to be drawn.

Primary CER involves the direct generation of clinical info on the relative merits or outcomes of one intervention in comparison to ≥1 others. Secondary CER involves the synthesis of primary studies to allow conclusions to be drawn.

Weighing the strengths and limitations of each type of comparative effectiveness research (CER) study.

Comparing Pragmatic vs. RCT and Observational study characteristics:

- **RCT** (Randomized Controlled Trial): Efficacy and safety; assess mechanistic effect; Can it work?
- **Pragmatic**: Effectiveness and safety; assess / inform decision-making; Does it work under usual care conditions?
- **Observational**: Effectiveness and safety; Does it work in actual practice?

- **Setting**: Ideal / artificial Real-world routine care (with potential minor departures) Real-world routine care
- **Population**: Strictly defined; homogenous Typically broad; heterogeneous Broad; heterogeneous
- **Randomization**: Yes Typically yes No
- **Blinding**: Typically yes No No
- **Interventions**: Fully interventional Minimally interventional (e.g., random) Non-interventional
- **Outcomes**: Clinical surrogates; short term Longer term outcomes; PROs Long term outcomes; PROs
- **Sample Size**: Typically small Typically larger Typically large
- **Validity**: High internal (↓bias); low external (↓generalizability) Moderate internal; moderate to high external Low internal; high external
- **Prospective/Retro**: Prospective Prospective Prospective or retrospective
- **Comparable cost**: Higher Moderate Lower

Examples of design: Adaptive design LST; adaptive design Database studies, cohort, case-control, cross-sectional

MCDA FOR HEALTHCARE

Multicriteria decision analysis (MCDA) is an application of analytical methods to help decision-makers to explicitly consider (qualitatively or/and quantitatively) multiple criteria to support their holistic integration to achieve a predetermined goal.
2. CRITERIA

Efficacy/effectiveness

DECISION CRITERIA

Qualitative criteria

“Doing what is best”

3. WEIGHTS

Greatest good for greatest number (utilitarianism)

Practical wisdom

A goodness (Virtue ethics)

4. EVIDENCE

Score

Low

High

5. PERFORMANCE

Maximize patient perceived health/reported outcomes

Maximize safety

6. QUALITATIVE IMPACTS

Awareness of common goal and specific interests

Wise use of resources (see economic criteria above)

Expert consensus

SCORES

1

2

3

4

5

The Trillion dollar questions

1. How to collect evidence on value and then incorporate this evidence into decisions on coverage, reimbursement, and payment for healthcare services?

2. How to develop value-based, cost effective healthcare that is trusted and not perceived as only cost cutting for profit/balancing federal budget?

3. Lack of evidence is a real impediment to value-based healthcare. Collecting this data will take time. Policy decisions based on incomplete data is subject to serious negative consequences. Half truth sometimes more dangerous than nothing.

Value Assessment Framework

Comparative clinical effectiveness

Incremental cost for better clinical outcomes (long-term)

Other benefits or disadvantages

Contextual considerations

“Care Value”

Public discussion and vote

Proven Health System Value

Maximizing Health System Value

Potential value of evidence

Public discussion

Comparative clinical effectiveness

Interim outcomes

Other benefits or disadvantages

Contextual considerations

“Care Value”

Public discussion and vote

Proven Health System Value

Maximizing Health System Value

Potential value of evidence

Public discussion
Comparative Clinical Effectiveness

- Comparative clinical effectiveness reflects a joint judgment of the magnitude of the comparative net health benefit and the level of certainty in the evidence on net health benefit.
- Patient groups inform what outcomes are important, differences across severity, time in disease course, etc.
- Patient groups inform re: opportunities for using or generating real-world evidence

Incremental Cost per Outcomes Achieved

- Long-term perspective on clinical outcomes and cost
- Costs from health system (payer) perspective – all health care costs
- Standard measures of health gain
  - Additional life-years gained
  - Improvement in quality of life
  - Cost per quality-adjusted life year gained, aka "cost per QALY"

Cost per QALY Thresholds

- Societal "willingness to pay"  
  - WHO 1-3x per capita GDP ($50,000-$150,000)
- Individual "willingness to pay"  
  - ~2 times annual salary ($100,000)
- "Opportunity cost" for the health system
  - ~1x GDP in UK, Latin America
  - Extrapolated ~$50,000 per QALY in the US
- ICER: $100,000-$150,000 per QALY

Other Benefits or Disadvantages

- Patient groups and others asked about benefits or disadvantages offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness.
  - Methods of administration that improve or diminish patient acceptability and adherence
  - Public health benefit, e.g. reducing new infections
  - More rapid return to work or other adverse effects on productivity (if not considered a benefit in cost-effectiveness)
- To be judged not by ICER but by one of its independent public appraisal committees

Contextual Considerations

- Contextual considerations include ethical, legal, or other issues that influence the relative priority of illnesses and interventions.
- Specific issue to be asked of patient groups and others:
  - Is this a condition of notably high severity for which other acceptable treatments do not exist?
  - Are other, equally or potentially more effective treatments nearing introduction into practice?
  - Would other societal values accord substantially more or less priority to providing access to this treatment for this patient population?
- To be judged not by ICER but by one of its independent public appraisal committees.
There are Multiple Value Frameworks

Net Health Benefit and Cost: the ASCO Framework
Two versions: advanced and curative contexts
Comparison in a trial: test vs standard

Cost (to system and to the patient)

Clinical benefit: OS>PFS>RR

Bonus: Extended survival

Toxicity: add points if less toxic, subtract if worse

Net Health Benefit

Calculating Clinical Benefit (modification)
JCO, July 2016

In a trial: treatment comparison

Step 1: Determine the regimen’s clinical benefit

1.A. Is Hazard Ratio (HR) for death reported?
YES. Assign an HR Score for death by subtracting the HR from 1, and then multiplying the result by 100. Write this number in the box labeled, “HR Score (death)”. Proceed to 1.F.

HR Score (death)

No. Proceed to 1B.

1.B. If HR for death is not reported, is median Overall Survival (OS) reported?
YES. Assign an OS Score by calculating the % difference in median overall survival between the two regimens. Write this number in the box labeled, “OS Score”. Proceed to 1.F.

OS Score

No. Proceed to 1.C.

1.C. If median OS is not reported, is Hazard Ratio (HR) for disease progression reported?
YES. Assign an HR Score for disease progression by subtracting the HR from 1, multiplying the result by 100, and then multiplying this number by 0.8. Write this number in the box labeled, “HR Score (progression)”. Proceed to 1.F.

HR Score (progression)

NO. Proceed to 1.D.

1.D. If HR for disease progression is not reported, is median Progression-Free Survival (PFS) reported?
YES. Assign an PFS Score by calculating the % difference in median progression survival between the two regimens. Multiply this number by 0.8. Write this number in the box labeled, “PFS Score”. Proceed to 1.F.

PFS Score

NO. Proceed to 1.E.

1.E. If median PFS is not reported, is Response Rate (RR) reported?
YES. Assign an RR Score by adding the complete response (CR) and partial response (PR) rates, and then multiplying this number by 0.7. Write this number in the box labeled, “RR Score.” Proceed to 1.F.

RR Score

1.F. Calculate the Clinical Benefit Score
Insert the HR, OS, PFS, or RR Score. Note: You should have a score for only 1 of the clinical benefit scales above. Write the total in the box labeled “Clinical Benefit Score”. The maximum allowable points are 80. Proceed to Step 2.

Clinical Benefit Score
Calculating Toxicity Score
(Modification) Grade and frequency matter

Calculating Net Health Benefit
Juxtaposed against Cost per Month

Calculating Bonus Points
Modification

NCCN Evidence Blocks

JCO, July 2016
Efficacy of Regimens Scale

<table>
<thead>
<tr>
<th>Score</th>
<th>Summary</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>Highly effective</td>
<td>Often provides long-term survival advantage or curative potential</td>
</tr>
<tr>
<td>4</td>
<td>Very effective</td>
<td>Sometimes provides long-term survival advantage or curative potential</td>
</tr>
<tr>
<td>3</td>
<td>Moderately effective</td>
<td>Moderately, mildly or unknown impact on survival but often provides control of disease</td>
</tr>
<tr>
<td>2</td>
<td>Minimally effective</td>
<td>Moderately, mildly or unknown impact on survival and sometimes provides control of disease</td>
</tr>
<tr>
<td>1</td>
<td>Palliative only</td>
<td>Symptomatic benefit only</td>
</tr>
</tbody>
</table>

Affordability of Regimens Scale

<table>
<thead>
<tr>
<th>Score</th>
<th>Summary</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>Very inexpensive</td>
<td>Affordability refers to overall cost of an intervention including drug cost, required supportive care, infusions, toxicity monitoring, management of toxicity, probability of care being delivered in the hospital</td>
</tr>
<tr>
<td>4</td>
<td>Inexpensive</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Moderately expensive</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Expensive</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Very expensive</td>
<td></td>
</tr>
</tbody>
</table>

ESMO Value Frameworks

Factors taken into account for ESMO-MCBS

- Overall survival, performance score
- Progression free survival
- Quality of life
- Magnitude of clinically benefit
- Toxicity
- Costs
- Will not be formally analyzed in view of significant heterogeneity across the ESMO-MCBS

Cherny, N et al, Ann Oncol. 30 May 2015
Considering the Several Frameworks?

- Shall we strive for a uniform approach to determining clinical benefit?
- Cross-trial comparisons are necessary if clinical benefit assessments are to have meaning.
- Reasonable cost: after accounting for net health benefit and cost threshold for value -- how much will we/can we spend for what degree of gain?
- Is there a role for value-based pricing?
- How to incorporate the value of agents/regimens into clinical pathways?
- Shared decision making

The Goal

- All patients with cancer will have lifelong access to high-quality, effective, affordable and compassionate care.
- The most accurate cancer information will be available so that patients and physicians can make informed decisions about cancer prevention and treatment (shared decision-making).
- The most accurate cancer information will be available so that policy makers will make informed decisions based upon the value to be delivered by cancer prevention and treatment.

Discussion

Good News….

Our future's so bright we gotta wear shades

Evidence as the Basis for Clinical Policy