Slide 1: Multilevel Interventions in Policy & Genomic Medicine

NCI Multilevel Interventions in Health Care: Building the Foundation for Future Research

E. Hawk, MD, MPH
UT MD Anderson Cancer Center
Duncan Family Institute

Las Vegas, Nevada
March 4-5, 2011

National Cancer Institute
U.S. Department of Health and Human Services
National Institutes of Health

Slide 2: 2011 - A Time of Incredible Change in Magnitude, Breadth, Depth, & Pace of American Health Care

- Poor public understanding of
  - Cancer and its cause
  - Risk & risk: benefit balance
- Poor public tolerance of
  - Complexity
  - Personal risk
  - Explosive technologic advances that pressure deliberative decision-making
  - IT (EMRs)
  - Communications
  - Imaging
  - Social connections
  - Molecular tools
- Transitioning of medical care system
  - Guidelines
  - Reimbursement reforms
  - Checklists
  - Specialization vs generalization
  - Health care systems
  - Need to demonstrate value = Quality/cost
- Universal cost-cutting

    - 2010 Health care reform = “I pay less/they pay more”
- Rising public expectations

Good Intention - Effective & efficient actions - Improved outcomes

Slide 3: Linking Multilevel Approaches to Issues in Health Policy – Warnecke, et al.

- Policies – tools often conceived at the national or state level to address a population concern
    - Always, well-intended
    - Hopefully, linked to evidence
    - Usually represent a compromise between science, fiscal concerns, and political maneuvering, and therefore, rarely the best of any of these
- Administration & implementation of policies can influence their ultimate impact on cancer incidence and outcomes at the local and individual levels
    - Access
    - Quality
    - Environmental stress
- The trans-level process of implementation (i.e., “signal transduction”) is critical to effectively link

Slide 4: Rising Disparities in Breast Cancer Mortality – What’s the Cause?

- Four possibilities:
    - Poor/limited access to screening mammography
    - Poor quality of screening
    - Poor quality of treatment
    - Biologic differences

Slide 5: A Remarkable Communal Approach to the Problem

- March 2006 – 102 individuals from 74 organizations form the Metro Chicago Breast Cancer Task Force
    - Health care providers
    - Administrators of safety net health care centers
    - Community leaders
    - Cancer survivors
    - Cancer organizations
    - Researchers

    - How did this form? Key champions? Aligned motives?
- October 2006 – task force report identifies 37 specific, pragmatic, evidence-based recommendations for policy changes to address local factors contributing to disparities
    - How were these identified, agreed upon?
    - Criteria? Roles/responsibilities?
    - Was this a MLI? Would it have been better if it was?

Slide 6: A Remarkable Communal Approach to the Problem

- March 2008 – Illinois General Assembly passes ground breaking legislation to reduce disparities
    - Elimination of co-pays and deductibles for mammograms
    - Patient navigation system
    - Were all TF recommendations incorporated? If not all, which?
    - Based on evidence that was generated and mentioned in the report, or independent of it?
- Follow-up
    - Was breast cancer mortality reduced? If not yet, when will we know?
    - Which elements of the intervention were most critical to success?
    - What, if anything, wasn't done as a result? Were the trade-offs worth it?
        - Childhood vaccination or obesity program
        - Tobacco cessation/quitline program
        - HPV vaccination
        - Prostate cancer screening
    - How should we think about prioritization of opportunities?

Slide 7: Multilevel Approaches and Challenges of Implementing Genomic Medicine – Khoury, et al.

- Rapid pace of discovery
- Long and complex translational paths to establish validity, especially against "hard" outcomes of greatest interest…those representing "clinical benefit"
    - Even in phases T0 & T1 alone
    - Later phases remain largely unexplored, but critical to success
- Opportunities far exceed investments
- Fundamentally, a problem of biomarkers

Slide 8: Possible Clinical Applications of Biomarkers

TYPE	APPLICATION	EXAMPLE
RISK or SCREENING	INDICATOR OF RISK OF DEVELOPING DISEASE	Cholesterol for CVD risk; PSA for prostate cancer
DIAGNOSIS	ONE MEASURABLE ELEMENT OF A PATHOLOGIC EVALUATION	c-kit for gastrointestinal stromal tumors[1]
PROGNOSIS	INDICATOR CORRELATED W/ OUTCOME IN UNTREATED PATIENTS OR W/ SURVIVAL OF HETEROGENEOUSLY TREATED PATIENTS	CA125 for overall survival and progression-free survival in ovarian cancer[2]
PREDICTION	MARKER THAT PREDICTS OUTCOME TO SPECIFIC TREATMENT	*KRAS* as predictor of efficacy of panitumumab/cetuximab in advanced CRC[3]; Oncotype DX in ER+/N- breast cancer
MONITORING/ SURVEILLANCE	MARKER TO ESTIMATE DISEASE STATUS FOLLOWING INTERVENTION	CEA in resected CRC
SURROGATE ENDPOINT	MARKER INTENDED TO SUBSTITUTE FOR A "CLINICAL BENEFIT" ENDPOINT	BP for CV mortality & morbidity;[4] tumor response

[1] *Anticancer Res 30:2407-2414, 2010*
[2] http://www.ovarianresearch.com/content/2/1/13
[3] *J Clin Oncol 27:4027-4034, 2009*
[4] The National Academies Press http://www.nap.edu/catalog.php?record_id=12869

Slide 9: Biomarkers in Cancer Screening

[image]
Article on "Mortality Results from a Randomized Prostate-Cancer Screening Trial" by Gerald L. Andriole, M.D.

For additional information contact: NCIDCCPSMLI@mail.nih.gov

[end image]

Slide 10: No Title

[image]
Article on "Mortality results from the Goteborg randomised population=based prostate-cancer screening trial" by Jonas Hugosson.

For additional information contact: NCIDCCPSMLI@mail.nih.gov
[end image]

Slide 11: Levels of Evidence Guiding Biomarker Utility – The Path to Validity

Level	Type of Evidence
1	• Single, adequately powered prospective study designed to test the marker; • Randomized controlled trial guided by the biomarker; • Meta-analysis or overview of LOE II/III studies; • Prospective trial with a primary objective of associating a marker and one or more clinical outcomes
2	Prospective therapeutic trial involving markers as a secondary objective
3	Large, retrospective studies evaluating associations in post-hoc analyses
4	Small retrospective studies; may be matched, case-control
5	Small pilot studies designed to estimate distribution of markers in a sample population; not designed to determine clinical utility

Hayes DF: Biomarkers in DeVita, Hellman & Rosenberg's Cancer: Principles & Practice of Oncology, 8th ed.; Lippincott Williams & Wilkins, 2008

Slide 12: Necessary Criteria for a Biomarker to Be Incorporated into Routine Clinical Use

1. Intended use clearly delineated
2. Magnitude of clinical outcomes associated with marker status sufficient to affect a clinical decision
3. Estimate of magnitude accurate, reliable, & validated
    - Assay technically stable, accurate, and reproducible

- Clinical study appropriately designed & powered to address the intended use and externally validated
- Analysis statistically rigorous

Slide 13: Clinical Activity in Biomarker Requests at MD Anderson Cancer Center FY01 to FY10

[image]
Line graph showing increase requests (actual) from Fiscal year 2001 to Fiscal year 2010 with a sharp increase from 2009 to 2010.

For additional information contact: NCIDCCPSMLI@mail.nih.gov

[end image]

Slide 14: Four Elements of Personalized Cancer Care Potentially Improved By Genomic Assessments

- Patient selection
  - Germline genetics & pharmacogenetics
- Target identification
  - Somatic genomics
- Environmental assessment
  - Lifestyle choices & exposures
- Agent(s) selection

Slide 15: "Infrastructures" Needed To Transform New Scientific Discoveries into Clinical Advances

- Internationally standardized, harmonized electronic medical records
  - Incorporating baseline/follow-up data on patients, treatments, outcomes
- Modernized clinical care guidelines incorporating standardized, serial sampling of patients and tumors with accommodation for fresh/frozen tissues
- Large, well-annotated repositories of blood, tissues, biospecimens
- "Hyper-specialization"

- Multi-institutional biospecimen-focused research consortia
- Innovative trial designs, including elements of adaptive randomization, biomarker-based eligibility, nested biomolecular analyses
- Recognition of time as one of the most critical and valuable components of medical research/care
- More inclusive, critical, and routine evaluations of risk/benefit and risk/risk
- Approaches to monitor and address the real possibility of increasing disparities in care as medicine incorporates more high-tech risk assessments and interventions

Slide 16: Multilevel Approaches and Challenges of Implementing Genomic Medicine – Khoury, et al.

- Because of the complexity, speed, potential for misunderstandings and miscommunications, as well as insufficient regulatory oversight involved in developing and applying genomic technologies in a world insufficiently prepared, there is the very real potential for INCREASED
    - Harms,
    - Worries,
    - Litigation,
    - Costs, and
    - Disparities
    - …without improving outcomes, at least uniformly.
- No clear or easy path forward

Slide 17: Tremendous Opportunities to Model the Necessary Connections to Facilitate Translational Progress Within Government

[image]
Showing connections; from top to bottom:

- N C I DCB
- N C I DCDT/DCP
- N C I DCCPS
- N I H
- F D A
- CDC
- A H R Q
- CMS

[end image]

Slide 18: Genomic Medicine & Multi-level Research - Great Challenges, Incredible Opportunities

"Nature is probabilistic and information incomplete, Outcomes are valued, Resources limited, …decisions unavoidable"

Weinstein MC & Fineberg HV
Clinical Decision Analysis. Saunders, London, 1980

[End Presentation]