Slide 1: Multilevel Interventions in Policy & Genomic Medicine

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

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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
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?

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?

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

<table>
<thead>
<tr>
<th>TYPE</th>
<th>APPLICATION</th>
<th>EXAMPLE</th>
</tr>
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<tbody>
<tr>
<td>RISK or SCREENING</td>
<td>INDICATOR OF RISK OF DEVELOPING DISEASE</td>
<td>Cholesterol for CVD risk; PSA for prostate cancer</td>
</tr>
<tr>
<td>DIAGNOSIS</td>
<td>ONE MEASURABLE ELEMENT OF A PATHOLOGIC EVALUATION</td>
<td>c-kit for gastrointestinal stromal tumors</td>
</tr>
<tr>
<td>PROGNOSIS</td>
<td>INDICATOR CORRELATED W/ OUTCOME IN UNTREATED PATIENTS OR W/ SURVIVAL OF HETEROGENEOUSLY TREATED PATIENTS</td>
<td>CA125 for overall survival and progression-free survival in ovarian cancer</td>
</tr>
<tr>
<td>PREDICTION</td>
<td>MARKER THAT PREDICTS OUTCOME TO SPECIFIC TREATMENT</td>
<td>KRAS as predictor of efficacy of panitumumab/cetuximab in advanced CRC ; Oncotype DX in ER+/N- breast cancer</td>
</tr>
<tr>
<td>MONITORING/ SURVEILLANCE</td>
<td>MARKER TO ESTIMATE DISEASE STATUS FOLLOWING INTERVENTION</td>
<td>CEA in resected CRC</td>
</tr>
<tr>
<td>SURROGATE ENDPOINT</td>
<td>MARKER INTENDED TO SUBSTITUTE FOR A “CLINICAL BENEFIT” ENDPOINT</td>
<td>BP for CV mortality &amp; morbidity; tumor response</td>
</tr>
</tbody>
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1 Anticancer Res 30:2407-2414, 2010
2 http://www.ovarianresearch.com/content/2/1/13
3 J Clin Oncol 27:4027-4034, 2009

Slide 9: Biomarkers in Cancer Screening

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

For additional information contact: NCIDCCPSMLJ@mail.nih.gov
Slide 10: No Title

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

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

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<thead>
<tr>
<th>Level</th>
<th>Type of Evidence</th>
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| 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

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

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

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

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

• Internationally standardized, harmonized electronic medical records
  o 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


• 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
  o Harms,
  o Worries,
  o Litigation,
  o Costs, and
  o Disparities
  o …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
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

[End Presentation]