Applied research for genomic applications in clinical practice

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What are "clinical genomic applications"?

AHRQ* definition of "genetic test":

"An analysis performed on human DNA, RNA, genes, and/or chromosomes to detect heritable or acquired genotypes, mutations, phenotypes, or karyotypes that cause or are likely to cause a specific disease or condition."

*Chin et al. Genetic Tests for Cancer. Technology Assessment prepared for the Agency for Health Care Research and Quality. January 9, 2006.

Broader definition of genetic tests

AHRQ definition also includes tests for gene products:

"A genetic test also is the analysis of human proteins and certain metabolites, which are predominantly used to detect HERITABLE or ACQUIRED genotypes, mutations, or phenotypes."

Purpose of genetic tests

AHRQ definition also specifies the applications of genetic tests:

"The purposes of these genetic tests include predicting risks of disease, screening of newborns, directing clinical management, identifying carriers, and establishing prenatal or clinical diagnoses or prognoses in individuals, families, or populations".

Purposes of Genetic Tests in Cancer Care

- Primary prevention:

  Detect inherited susceptibility to initiate prophylactic interventions (surgery/drugs/earlier screening)

- Secondary prevention:

  Early detection of cancers in asymptomatic carriers

- Diagnosis and treatment:

  Molecular diagnosis, evaluate prognosis, detect recurrence, monitor patient or tumor response to treatment

What genetic tests are available for cancer care?

- AHRQ Technology Assessment lists 62 clinically available genetic tests mainly for 9* solid or hematological tumors:
  - 5 (8%) for primary prevention
  - 11 (18%) for early detection
  - 54 (87%) for diagnosis and management

  (some overlap so sum > 62)

*sites=breast, prostate, lung, colorectal, pancreas, ovarian, liver, lymphoma, leukemia

Examples of Genetic Tests in Cancer Care

- Primary prevention:

  BRCA1/2 (breast/ovarian cancer risk)

  Secondary prevention:

  PSA (prostate cancer screening)

  Diagnosis and treatment:

  (of metastatic breast cancer)

  HER 2 Neu (eligibility for Herceptin Rx)

  Onco*type* DX (more aggressive chemotherapy)

Genetic vs. Genomic

- Genetic refers to a specific gene whereas genomic refers to large numbers or all genes.

- However, AHRQ report eliminates the divide:

  "We have found that the term 'genetics' and 'genomics' are often used interchangeably in the literature and both can refer to tests for molecular or biochemical markers, as well as cytogenetic and gene-based tests."

More Genomic Applications

- Genetic tests have maximum clinical utility if a follow-up intervention is available to block or minimize the effects of deleterious genes
- Some interventions rely on genomic technologies and therefore could be considered genomic applications

Targeted Therapies

- Targeted therapies are drugs and vaccines that act with specificity on a gene, gene product, or gene function to block the growth and spread of cancer.

Examples:

Monoclonal antibody drugs

http://www.cancer.gov/cancertopics/factsheet/Therapy/biological

Small molecule and apoptosis inducing drugs

http://www.cancer.gov/cancertopics/factsheet/Therapy/targeted

Pipeline Genomic Applications

- Genetically engineered vaccines*
- Molecular/functional imaging to visualize gene function and drug action*
- Family history tools; risk/prognostic algorithms*
- nanoparticle receptor-mediated drug delivery*
- Gene therapy (e.g.siRNA); Other?

*some applications available now

Clinical Genomic Applications

Tests, drugs, devices, or other technologies that enable the clinical characterization and management of genes, gene products, or genetic pathways.

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Some major goals of applied research at NCI (http://appliedresearch.cancer.gov)

- Assess net benefit of cancer prevention and control interventions in community care:
  - trends in cancer incidence, mortality, survival, and quality of life, in relation to:
    - risk factors, health care utilization, quality of care, economic burden, and other determinants;
- Assess effectiveness of routine community care:
  - is adequate care being delivered to the appropriate target populations?
    - What are barriers?
    - What are facilitators?

Translation of Genomic Applications into Clinical Care

NCI Grants Portfolio on Delivery-Oriented Research, 2000-2006*

- Only 12 grants related to delivery of care involving genomic applications
- Most of the 12 focused on BRCA1/2 testing
- Total costs=$12 million

*Conducted by Anita Ambs, MSPH;
Applied Research Program

Consequences of Applied Research Gaps

Technology assessments hampered, so limited framework for developing:

- Evidence-based standards of care
- Public or private insurance coverage policy

More Consequences of Applied Research Gaps

- Quality assurance efforts hampered due to:
  - Lack of specific measures to assess quality of care
  - Lack of surveillance data to monitor care and possible disparities
  - Lack of data on interventions to improve care

Consequences of Applied Research Gaps

Access to care* not monitored adequately

Persisting inequities can lead to disparities in population measures of effectiveness

INCIDENCE	MORTALITY
SURVIVAL	QUALITY OF LIFE

*one indicator of quality

What are the dimensions of access to care?

- Affordability
- Availability
- Accomodation of practice to patient constraints and preferences
- Acceptability
- Access by the target populations

Ref: Penchansky R and Thomas JW. The concept of access: definition and relationship to consumer satisfaction. Medical Care 19 (2): 127-140, 1981.

Case Study #1: Affordability

Adjuvant monoclonal antibody therapies for metastatic colorectal cancer are very costly;

Added survival time or time till progression is measured in months (i.e., 4-5 median).

Ref: Meropol NJ and Schulman KA. Cost of cancer care: issues and implications.

Cost of metastatic CRC Rx per 6 months for 70 kg patient (1.7 sq meters body surface)

- Cytotoxics = fluorouracil (FU), leucovorin (LC), irinotecan (IR), capecitabine, oxaliplatin (OX)
- Monoclonal Abs = bevacizumab, cetuximab, panitumumab

Regimen	Cost
FU + LC	$96
Add IR or OX	Add $20,000-$30,000
Add bevacizumab (Avastin®)	Add $24,000
Add cetuximab (Erbitux®)	Add $52,000

Case Study #2: Availability

NCI Physician Survey on Genetic Testing for Cancer Susceptibility

- 1999-2000 national probability survey (n=820 primary care;431 cancer care);
- Response rate = 71%

Ref: Wideroff L, Freedman AN, Olson L, Klabunde CN, Davis W, Srinath KP, Croyle RT, Ballard-Barbash R. Physician Use of Genetic Testing for Cancer Susceptibility. Cancer Epidemiol Biomark Prev 12: 295-303, 2003.

Have you ever ordered genetic tests or referred patients elsewhere for testing or risk assessment?

- Use was highest among physicians who had local testing and counseling facilities [46.9% (95% CI, 42.6–51.2)];
- intermediate among those without such facilities [31.8% (95% CI, 24.2–39.4)];
- lowest among those who were unsure whether there were local facilities [11.6% (95% CI, 8.3–14.9)].

Case Study #3: Accomodation

- NCI physician survey:

  Having patients who asked whether they can or should get tested was the factor most strongly associated with physician use of tests:

  OR = 5.52* (95% CI, 3.97–7.67%)

  *adjusted for practice location, feeling qualified to recommend tests, receiving advertisements, awareness of testing/counseling facilities.

Case Study #4: Acceptability

Many studies have reported variation in the acceptability of BRCA 1 and 2 counseling and testing (lower among African-Americans)

A small California study recently reported relatively high levels of acceptability and compliance among an underserved Latina community

If we build it will they come?

- Following cancer genetics CME of physicians in 2 indigent health care systems in California, quality referrals to genetics clinics increased.
  - **88% of referred patients (n=77, predominantly Latina) kept their appointments.**
  - **The majority expressed satisfaction and reduction in anxiety.**

Ref: Ricker C, Lagos V, Feldman N, et al. If we build it will they come? Establishing a cancer genetics services clinic for an underserved predominantly Latina cohort. J Genet Couns 15: 505-514, 2006.

Case Study #5: Access by target populations

Do we know the right target populations for genomic technologies?

- Genomic applications expand the criteria of target populations beyond demographic and histologic variables to include genetic susceptibility due to inherited or somatic factors.

Metastatic colorectal cancer Rx

Patients who are homozygous for the UGT1A1*28 allele have an increased risk of developing severe neutropenia when receiving irinotecan, especially the 300-350- mg/m2 regimen.

The Invader UGT1A1 Molecular Assay identifies the at-risk subgroup and can be used by health care professionals to help guide irinotecan-treatment decisions.

Defining target populations through metabolic phenotyping

- Roche Amplichip CYP450
  - Tests 27 alleles in CYP2D6 and CYP2C19 genes
  - Classifies people into extensive and poor metabolizers of many kinds of drugs.

Ref: Report by Cigna Healthcare

www.cigna.com/.../coverage_positions/medical/mm_0381_coveragepositioncriteria_AmpliChip.pdf

Where do we go from here?

What can the research community do to improve understanding of delivery of genomic applications?

- net benefit
- effectiveness

Delivery-oriented research is needed to understand:

- Who are the target populations and what are their preferences?
  - Epidemiologic research (more clinical trials, molecular epidemiology, post-marketing surveillance, etc.)
  - Behavioral research (patient and provider preferences, behavioral determinants of utilization)

Delivery-oriented research is needed to understand:

- If appropriate care is being provided to the target populations (i.e., effectiveness):
  - Health services research (patterns and determinants of access to care, quality of care, organizational and policy changes needed);
  - Surveillance (trends in incidence, mortality, survival, quality of life)

Delivery-oriented research is needed to understand

- What are cost benefits?*
  - health economics research (incremental costs, cost-effectiveness, cost-utility, etc.)
  - policy research (public and private insurance coverage, etc.)

*Is this the bottom line for access to expensive genomics applications?

A few good introductory refs about health economic measures

- Primer on cost-effectiveness analysis (American College of Physicians, 1999-2000) http://www.acponline.org/journals/ecp/sepoct00/primer.htm

- Phillips KA, Veenstra D, Van Bebber S, Sakowski J. An introduction to cost-effectiveness and cost-benefit analysis of pharmacogenetics. Pharmacogenomics 4:231-239, 2003.

Conclusions

Marketing of genomics applications does not guarantee effectiveness in routine community care.

We need to fill in the gaps in delivery-oriented research to better understand how to implement clinical genomic applications.

Conclusions

Ultimately, the successful implementation of clinical genomic applications requires that we influence the patient, provider, health care, and societal factors that contribute to effectiveness in routine community care.