IOM-NCPF Workshop
Policy Issues in the Development of Personalized Medicine in Oncology

CDC Initiative in Assessment of Genomics Tests

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June 8, 2009, Washington, DC
Outline

Context of CDC Evaluation Initiative

Evolution of Initiative

Evaluation Methods & Procedures

Oncology-related reviews & recommendations

Potential policy issues for development of personalized medicine in oncology
Advances in Genetics/Genomics Research in Cancer

HuGE Publications in Studies of Colorectal Neoplasms (A Temporal Trend and Spatial Pattern)

Phenopedia

Prostatic Neoplasms

Related Diseases

Summary

283 genes have been reported with Prostatic Neoplasms

huangenavigator.net/ (April 28, 2009)
Rapid Translation to Practice
e.g., Web-available Cancer-Related Testing

*G-nostic*: Smoking Cessation

*MyGenome*: Drug Metabolism/Sensitivities

*DNA Direct*:
- Risk prediction/screening
- Disease screening
Uncertainty in Process & Oversight for Genomic Test Development, Translation

Development process for diagnostics, markers, genomic tests, not well defined

Oversight of tests complex, many responsible parties with “significant gaps” that “could lead to harms”

IOM Cancer Biomarkers 2007
SACGHS. U.S. System of Oversight of Genetic Testing, April, 2008: oba.od.nih.gov/sacghs/
What Consequences of Rapid Translation of Genetic Testing?

New England Journal of Medicine

Letting the Genome out of the Bottle — January, 2008
Will We Get Our Wish?
David H. Hamer, M.B., B.S., Sc.D., M.P.H., Marn J. Khoury, M.D., Ph.D., and Jeff

It may happen soon. A patient, perhaps one you have known for years, who is overweight and

Washington Post

My genome. So what?

Research is needed into the way individuals use their genomic information, and into protection from its abuse by others.

nature

Vol 456 | Issue no. 7218 | 6 November 2008

My genome. So what?

Human genome research has proved itself predictably unpredictable. As was widely
Potentially Unanswered Questions about Genetic Tests in Translation

How valid and reliable are the genetic/genomic tests (analytic validity)

How well do they predict outcomes (clinical validity)

What are the benefits and harms, what actions to take (utility)

How should the medical community, public health, policy makers respond
Currently, Limited Published Research for Evaluation & Implementation

T0 ↔ T1 ↔ T2 ↔ T3 ↔ T4

Discovery to Application to Guideline to Practice to Population Health Impact

Bench to Bedside Continuum early phases only

Amount of published research

↑ Population Health Benefit

97% of genetics research publications in T0 & T1

Translation of genetic testing to practice in context of other health services in U.S.

Healthcare Spending High, Record $2.2 Trillion in 2007 ~16% of GDP

U.S. behind many advanced countries in health

~55% of Americans receive recommended care for acute or chronic conditions, ~50% receive recommended preventive care

~20%-30% receive contraindicated care

~30- 40% of dollars spent on overuse, underuse, misuse of services, etc.

Where does & how should genetic testing fit?

Genomic tests, ready for use?

Evaluation of Genomic Applications in Practice and Prevention

Purpose:
Establish & test a systematic, evidence-based process for evaluating genetic tests and other applications of genomic technology in transition from research to practice

www.egappreviews.org/
cdc.gov/genomics/gtesting/
Evolution of EGAPP

Development shaped by a number of U.S. & International meetings & reports

1994  US IOM  Assessing Genetic Risks

1997-2008  US HHS Advisory Committees on genomics & health
http://www4.od.nih.gov/oba/sacghs.htm

2003-2008  EU & OECD meetings & reports on evaluation & quality assurance
EGAPP

Non-regulatory CDC-supported initiative
Develop process for evaluation
Evidence-based, transparent, publicly accountable
Integrate existing processes for evaluation
Minimize conflicts of interest
Independent multidisciplinary Work Group composed of non-federal experts to develop methods, make recommendations
Steering Committee of federal agencies Stakeholder Group for consultation, evaluation

cdc.gov/genomics/gtesting/
EGAPP Approach: Methods expanding from other processes, methods

U.S. Preventive Services Task Force
www.ahrq.gov/clinic/uspstf07/methods/benefit.htm

Centre for Evidence-Based Medicine
http://www.cebm.net/

Agency for Healthcare Research & Quality Evidence-based Practice Center Program
www.ahrq.gov/clinc/epc/

QUADAS [BMC Medical Research Methodology 2003, 3:25]
www.biomedcentral.com/1471-2288/3/25

FDA, others
cdc.gov/genomics/gtesting/

Teutsch SM et al. Genetics In Medicine 2009;11:3-14
44 questions for evaluation of genetic tests
Common Procedures for Evidence-based Recommendations, USPSTF & EGAPP

Published, transparent methods & procedures

Recommendations based on scientific evidence, not expert opinion

Use of analytic frameworks to link pathway from health service to health outcomes & to link direct & indirect evidence to key questions in pathway

Comprehensive, systematic, & objective search for & review of evidence with grading of evidence quality

Transparent, explicit linkage of evidence to recommendation

Common Procedures for Evidence-based Recommendations, USPSTF, EGAPP (2)

Technical experts primarily as consultants & reviewers, not decision-makers

Peer review of evidence reviews & of recommendations by experts & stakeholders

Final evaluation & recommendations from independent panel, experts in evidence-based processes, minimize conflicts of interest

Recommendation based on overall evaluation of benefits & harms; strength of recommendation based on evidence quality

*AJPM* 2001;20(s3):21-35; *AJPM* 2000;18(1s):35-91
*Gen Med* 2009;11:3-14
EGAPP Evaluation

Careful, explicit, specific definitions of disorder, genetic test & clinical setting

Evaluation of accuracy & reliability in detecting genomic markers of interest (analytic validity)

Evaluation of accuracy & reliability of test in predicting disorder or phenotype of interest (e.g., drug response) (clinical validity)

Gen Med 2009;11:3-14
EGAPP Evaluation

Evaluation of evidence of improved health outcomes from test & interventions, utility in decision-making (clinical utility)

Assessment of contextual factors, such as alternative approaches, costs

Overall assessment of benefits & harms

*Gen Med* 2009;11:3-14
Recent EGAPP Recommendations
Genetics in Medicine January 2009

EGAPP Recommendation Statement

Recommendations from the EGAPP Working Group:
can tumor gene expression profiling improve outcomes
in patients with breast cancer?

Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group*

Recommendations from the EGAPP Working Group:
can UGT1A1 genotyping reduce morbidity and mortality
in patients with metastatic colorectal cancer treated
with irinotecan?

Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group*

Recommendations from the EGAPP Working Group:
genetic testing strategies in newly diagnosed individuals
with colorectal cancer aimed at reducing morbidity and
mortality from Lynch syndrome in relatives

Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group*

www.egappreviews.org/
Breast Cancer Gene Expression Profiles

Application: Prognostic, Used in Treatment Decisions

Population: Women with stage I or II, node negative breast cancer (estrogen receptor status variable, depending on test)

Summary Statement: The EGAPP Working Group found insufficient evidence to make a recommendation for or against the use of tumor gene expression profiles to improve outcomes

## Breast Cancer GEP Evidence Overview

<table>
<thead>
<tr>
<th>Test</th>
<th>Analytic Validity</th>
<th>Clinical Validity</th>
<th>Clinical Utility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oncotype DX</td>
<td></td>
<td>Adequate Evidence (assoc. of recurrence score with recurrence &amp; response to chemotherapy)</td>
<td>Inadequate Evidence</td>
</tr>
<tr>
<td>Mamma Print</td>
<td>Inadequate Evidence</td>
<td>Adequate Evidence (association with future metastases)</td>
<td>No evidence</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inadequate Evidence (to assess added value to standard risk stratification)</td>
<td></td>
</tr>
<tr>
<td>H:1 Ratio Test</td>
<td></td>
<td>Inadequate Evidence</td>
<td>No evidence</td>
</tr>
</tbody>
</table>
Breast Cancer Gene Expression Profiles
Considerations for Practice

Preliminary evidence of potential benefit of Oncotype Dx testing for some women who face decisions about treatment options (reduced adverse events for low risk women avoiding chemotherapy)

Could not rule out the potential for harm for other women (breast cancer recurrence that might have been prevented)

Clinicians decide on a case by case basis if use of GEP adds value beyond current prognostic markers, how to weigh benefits & harms, & if relevant to patient

If GEP used, counseling & educational materials provided to patient to address potential benefits/harms & how results may affect decisions regarding therapy
Breast Cancer Gene Expression Profiles

Research Needs

Clinical validation studies to include tests available to typical patient populations, relevant ethnic groups, and calibration against actual observed risk.

Clinical trials to understand impact of chemotherapy on outcomes of women classified into low, intermediate, & high risk groups (e.g., current TAILORx), particularly for impact on women at low risk to evaluate benefits/harms from foregoing therapy.

Pre-analytic issues related to sample preparation.

Analytic validity of tests, including external proficiency testing & high volume applications.
UGT1A1 Genotyping

Application: Pharmacogenomic

Population: Patients with metastatic colorectal cancer to be treated with irinotecan

Summary Statement: The EGAPP Working Group found that evidence is insufficient to recommend for or against routine use of UGT1A1 genotyping in patients with the intent of modifying the dose as a way to avoid adverse drug reactions (severe neutropenia)

UGT1A1 Genotyping
Research & Practice Considerations

*28 allele associated with slower metabolism of irinotecan &, at given dose, more adverse side effects, better tumor response, better survival
Unclear if benefits of reduced adverse drug events from modified treatment outweigh harms of poorer survival
Testing may assist patients in choosing improved quality of life or better survival
Research needed: Rigorous evaluation of genotyping using irinotecan treatment protocols
Testing for Lynch syndrome in individuals with newly diagnosed colorectal cancer

Application: Diagnostic

Population: Individuals with newly diagnosed colorectal cancer (CRC)

Summary Statement: The EGAPP Working Group found sufficient evidence to recommend offering genetic testing for Lynch syndrome to newly diagnosed individuals to reduce morbidity and mortality in relatives, but insufficient evidence to recommend a specific genetic testing strategy among the several examined.

Stakeholder Response to EGAPP
Generally Positive

“HHS should create and fund a sustainable public/private entity of stakeholders to assess the clinical utility of genetic tests (e.g. building on CDC’s Evaluation of Genomic Applications in Practice and Prevention [EGAPP] initiative).”

U.S. System of Oversight of Genetic Testing:
A Response to the Charge of the
Secretary of Health and Human Services
Report of the Secretary’s Advisory Committee
on Genetics, Health, and Society

April 2008
Stakeholder Response to EGAPP
Generally Positive (2)

Response: The MEDCAC consensus is that the desirable characteristics of evidence for diagnostic genetic testing are not different from the desirable characteristics of diagnostic testing in general. The panel felt that the evidence should be rigorous, and noted that genetic testing has potential harms as well as potential benefits, and that the public is served by robust evidence. The panel also noted that, as with other diagnostic testing, determining the acceptable level of evidence may be interpreted within the context of specific diseases, specific treatments and specific tests. The MEDCAC consensus is that the EGAPP-identified ACCE (Analytic and Clinical validity, Clinical utility and associated Ethical, legal, and social implications) criteria are a desirable framework for this use. See Teutsch SM et al. (2009), in particular Tables 3 and 4 from that article. Note: EGAPP is the Evaluation of Genetic Applications in Practice and Prevention working group, supported by the Centers for Disease Control and Prevention's National Office of Public Health Genomics.
Increasing Communications to Improve Translation

Clinical, Public Health, & Community Practice

Translation Programs

Network of Stakeholders

Knowledge Synthesis

Translation Research

Determining & sharing what is known & not known & how it’s known

Research to fill Knowledge Gaps

Genomic Applications In Practice & Prevention Network (GAPPNet)

Evidence Based Recommendations

Linking Evidence to Practice Guidance in a Transparent & Credible Way
Networking Stakeholders
NIH/CDC Personal Genomics Workshop

Agreement on Broad Recommendations:
Development of standards for assessment
Multidisciplinary research to fill knowledge gaps on validity, utility
Credible knowledge synthesis & dissemination to researchers, clinicians, public
Linkage of science to evidence-based recommendations
Assessment, evaluation of criteria for personal utility in addition to clinical utility

Khoury Genetics in Medicine 2009 In Review
NCI-CDC Collaborative Examination of Cancer Genomics Funding

Discovery to Application → Application to Guideline ↔ Guideline to Practice ↔ Practice to Population Health Impact

NCI funding for genomics research??

Schully SD, Khoury MJ, Pub Health Genomics Submitted
Recent NIH/NCI Funding Opportunity in Translation: Comparative Effectiveness

NCI Guidelines for ARRA Research and Research Infrastructure Grand Opportunities: Comparative Effectiveness Research in Genomic and Personalized Medicine

Announcement Number: RFA-OD-09-004

Areas of Scientific Priority:

Advances in cancer genomics and the recent progress in identifying susceptibility genes for a wide variety of cancers are ushering in a new era of personalized cancer care and prevention. Using pharmacogenomic testing, we expect that cancer drugs could become tailored by genetic backgrounds to minimize adverse effects and increase treatment effectiveness. Moreover, stratification of cancer risk using biological markers such as genetic variants and protein markers are expected to increase early detection and primary prevention efforts. Gene expression profiles in tumors may become prognostic markers that could direct personalized chemotherapies and other interventions. Several examples of genetic risk on stratification for treatment and prevention are already available in breast cancer, colorectal cancer, prostate cancer and leukemias. Nevertheless, to date, there has been no systematic research conducted to compare the clinical effectiveness and cost-effectiveness of cancer care and prevention based on genomic tools and markers compared to existing standards of care and prevention that do not use genome-based approaches. Without such research, the promise of genomics and personalized medicine may not be fulfilled.
Potential Policy Issues

Improved oversight, e.g., SACGHS U.S. System of Oversight of Genetic Testing, April, 2008

Defining translation pathway (validity, utility) e.g., IOM Biomarkers 2007; Khoury 2007; Woolf 2008

Defining evidence standards

Research evaluating validity & utility (v. discovery)

Knowledge synthesis, systematic evidence-reviews (v. novel findings)

Research addressing Knowledge Gaps

Implications for family members of some “personalized” genetic testing, such as Lynch
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CDC Initiative in Assessment of New Tests

Information: cdc.gov/genomics

Contact: RCoates@cdc.gov

The findings and conclusions in this presentation are those of the author and do not necessarily represent the views of the Centers for Disease Control and Prevention.