Evidence-based medicine and genomic medicine programs: Lessons from EGAPP

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Chair, EGAPP Working Group
President and CEO, The Colorado Trust
Outline

- The EGAPP approach to evidence-based genetic testing
- Barriers and challenges in using evidence-based methods in genomics
- Potential solutions
- Opportunities for the future
Questions about genetic testing

• How valid and reliable are available genetic tests and how well do they predict outcomes?
• What are the benefits and harms associated with the clinical use of these tests?
• What actions should be taken based on results?
• How should the medical community, public health, policy makers respond?
EGAPP

Evaluation of Genomic Applications in Practice and Prevention

- CDC initiative with steering committee from other federal agencies
- Non-regulatory
- Independent, non-federal, multidisciplinary Working Group
- Integrate existing processes for evaluation and appraisal
- Minimize conflicts of interest
- Evidence-based, transparent, and publicly accountable

www.egappreviews.org
EGAPP Working Group approach

- Integrate knowledge and experience from existing processes
  - Genetic test assessment framework from ACCE
  - Assessment of quality of individual studies, adequacy of evidence, and level of certainty of net benefit (benefits minus harms) from USPSTF
  - Systematic evidence review and evidence syntheses process from AHRQ’s Evidence-based Practice Center (EPC) program and in-house reviews
- New modeling methods to address evidence gaps
- Develop clinical recommendations with clear linkage to the evidence
Steps in the EWG process

- Select topic: genomic application to be evaluated
- Define the clinical scenario for use of the genetic test
- Create an analytic framework of key questions to guide the evidence review
- Find, evaluate the quality and adequacy, and synthesize the existing literature
- Determine the net benefit (benefit minus harms) of the clinical application of the test
- Create a recommendation based on the certainty of net benefit
Key questions in analytic framework

- **KQ 2: Analytic validity**
  > Is the test reliable, accurate, reproduceable?

- **KQ 3: Clinical validity**
  > Do test results translate to something with clinical importance? (disease risk, drug metabolism or response, etc.)?

- **KQ 4: Clinical utility**
  > Does use of the test in clinical decision-making translate to an important health outcome? Are any harms (KQ 5) outweighed by the benefits?
Recommendation statement

Recommendations from the EGAPP Working Group: testing for cytochrome P450 polymorphisms in adults with nonpsychotic depression treated with selective serotonin reuptake inhibitors

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

This statement summarizes the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group recommendations regarding CYP450 genetic testing in adult patients beginning treatment with selective serotonin reuptake inhibitors (SSRIs), and the supporting scientific evidence. EGAPP is a project developed by the National Office of Public Health Genomics at the Centers for Disease Control and Prevention to support a rigorous, evidence-based process for evaluating

- Evidence is insufficient evidence to support a recommendation for or against CYP450 testing to inform SSRI therapy, use is discouraged until further clinical trials are completed
Barriers and challenges

- Significant evidence gaps
  - Analytic validity--lab-developed tests, proprietary interests, insufficient regulation
  - Clinical validity--mainly associational studies
  - Clinical utility--very few randomized controlled trials of efficacy in clinical use
  - Net benefit--little attention to possible harms
The Genomics Evidence Gap

Health Affairs 2009

The Evidence Dilemma In Genomic Medicine

We need a roadmap for the appropriate integration of genomic discoveries into clinical practice.

by Muin J. Khoury, Al Borg, Ralph Coates, James Evans, Steven M. Teutsch, and Linda A. Bradley

ABSTRACT: An ongoing dilemma in genomic medicine is balancing the need for scientific innovation with appropriate evidence thresholds for moving technology into practice. The current low threshold allows unsubstantiated technologies to enter into practice, with the potential to overwhelm the health system. Alternatively, establishing an excessively high

NEWSFOCUS

JAMA 2008

Closing the Evidence Gap in the Use of Emerging Testing Technologies in Clinical Practice

Kathryn A. Phillips, PhD

There is no consensus about optimal testing methods. Guidelines recommend using either immunohistochemistry with indeterminate results confirmed by fluorescence in situ hybridization (FISH), or FISH to determine HER2 status. Although FISH is a better predictor of response to

Science 2011

Waiting for the Revolution

Having the complete human DNA sequence hasn’t yet produced big advances in primary medicine, prompting some to ask what’s delaying the genomic revolution in health care?

IN 2009, THE SCHOOL OF MEDICINE AT Johns Hopkins University turned itself inside out for the human genome. Although ranking consistently among the top medical schools in the United States, it scrapped the existing curriculum and installed a shiny new “Genes to Society” agenda over the summer. A committee slotted genetics into every nook and cranny of the school’s 4-year program. Edward Miller, dean and CEO of Johns Hopkins Medicine, who backed the change, said at the time, “It’s the smart thing to do.”

Of course, it’s been smart not to do it.

Association members last year found that only 10% of respondents thought they had enough knowledge to use gene tests in prescribing medicines, although nearly all thought such tests were useful. DNA testing is growing rapidly in oncology to guide the treatment of some cancers, and in screening couples before conception and newborns to find dangerous mutations. Based on recent studies of cancer cell genetics, many labs are developing therapies to narrow a target tumor DNA. But aside from these situations, applications are scant, most public health reviews of DNA-based approaches have not found a health benefit.

As doctors and scientists look back over the decade since the human genome was published, some are asking tough questions. Is the translation of DNA research into medical practice taking longer than expected? Has the genomic medicine revolution faltered?

Such questions can elicit a sharp response from leaders in clinical genomics. Eric Topol, a pioneering researcher on DNA-related treatments in cardiovascular dise.
Barriers and challenges

- **Volume of tests**
  - Over 2,000 mostly single gene disorders (Genetests-and Genetic Testing Registry)
  - More than 200 new Omic tests since 2009 (CDC GAPPFinder)

- **Evidence review, synthesis and translation is time and resource intensive**

- **Whole genome sequencing**
  - Additional problems of incidental mutations, nonsense mutations, volume of information
Barriers and Challenges

- Research and researcher interests
- Support for innovation
- Industry interests and direct-to-consumer advertising
Barriers and challenges

- GWAS and the problem of small associations
- Improvements at the margins of usual care
Barriers and Challenges

● New ethical, privacy, and informed consent issues:
  » Carrier status testing
  » Selective return of results to individuals
  » Population/longitudinal studies
Potential solutions

- Rapid assessment for “insufficient evidence”
- Provide clear research paths to fill in gaps
- Provide recommendations for “actionable” results (good evidence on CV, insufficient for CU)
- Innovative study design approaches
- Collaborative networks
  - Laboratory
  - Clinical studies
Opportunities

- Tiers and Bins: classification systems with clear links to needed research and to clinical use
Three-Tier Classification of Recommendations on Genomic Applications

- **Tier 1**: Ready for implementation (per evidence-based recommendation on clinical utility)

- **Tier 2**: Informed decision making (adequate information on analytic and clinical validity, promising but not definitive information on clinical utility)

- **Tier 3**: Discourage use (no or little information on validity or utility; or evidence of harm)

  - Khoury MJ et al. Genetics in Medicine 2010
Binning the Human Genome
Based on Evidence base and type of Application

<table>
<thead>
<tr>
<th>Criteria:</th>
<th>Clinical Utility</th>
<th>Clinical Validity</th>
<th>Unknown Clinical Implications</th>
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<tbody>
<tr>
<td>Genes:</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Bins:</td>
<td>Bin 1 Medically actionable incidental information</td>
<td>Bin 2A Low risk incidental information</td>
<td>Bin 2B Medium risk incidental information</td>
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<tr>
<td>Examples:</td>
<td>BRCA1/2 MLH1, MSH2 FBN1 NF1</td>
<td>PGx variants and common risk SNPs</td>
<td>APOE Carrier status for recessive Mendelian disorders</td>
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<tr>
<td>Estimated number of genes/loci:</td>
<td>10s (eventually 100s – 1000s)</td>
<td>1000s</td>
<td>10s</td>
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Alleles that would be reportable (YES) or not reportable (NO) in a clinical context

<table>
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<tr>
<th>Variants</th>
<th>Known deleterious</th>
<th>Presumed deleterious</th>
<th>VUS</th>
<th>Presumed benign</th>
<th>Known benign</th>
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<tr>
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<tr>
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<td>NO ²</td>
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</tbody>
</table>

--Berg, Khoury, Evans Genetics in Medicine 2011
Applicability of EGAPP methods in WGS and binning

- Poor evidence for analytic validity: must be addressed by NGS methodology
- Poor evidence for clinical validity: assign to Berg/Evans Bin 3, Khoury tier 3 (don’t report, don’t use clinically, needs more research)
- Evidence for clinical validity, poor evidence for clinical utility: assign to Bin 2/tier 2 (conditionally report and or use clinically, needs more research)
- Evidence for clinical utility: assign to Bin 1/tier 1 or tier 3 (report and use if benefit, don’t if no benefit or net harm)
Comparative effectiveness, marginal costs, harms and benefits

- Does the availability and use of individual genetic information improve health outcomes in terms of net benefit (benefits minus harm) when compared to usual care? (marginal benefit)
- Is the marginal improvement in benefit (above that of usual care) worth the costs and harms?
Can we Have our Genome and Eat it Too? Deploying the Whole Genome Sequence In Medicine and Public Health, One Base Pair At A Time.

Categories: genomics, whole genome sequence

November 3rd, 2011 9:56 am ET - Muin J Khoury, Director, Office of Public Health Genomics, Centers for Disease Control and Prevention

The popular proverbial saying “you cannot have your cake and eat it too” implies that one cannot consume something and preserve it at the same time—in other words, we cannot have it both ways. Well, for once, maybe we can have our cake—our whole genome sequence (WGS)—and eat it too. I believe having our WGS and consuming it in small bite sizes over a lifetime may be the only way to integrate it into medicine and public health.

Rapid advances in genomic sequencing technologies are making the possibility of reliable and affordable whole genome sequencing (WGS) a reality in the next few years. We all carry about 6 billion base pairs of DNA in each of our cells, with 5-10 million inherited variants that are