Current approached for evaluating genetic variants for clinical use

EGAPP: Evaluating Genomic Applications in Practice and Prevention

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President and CEO, The Colorado Trust
Unanswered 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?
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 Berg, 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 threshold would discourage the rapid proliferation of technologies in clinical practice.

JAMA 2008
Closing the Evidence Gap in the Use of Emerging Testing Technologies in Clinical Practice

Kevin A. Phillips, PhD

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 therapy, it is more expensive and does not offer the advantage of screening for mutations in the gene that may lead to resistance.

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 finest thing to happen to the School of Medicine.”

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 disease, said, “We need to quit trying to push genetics into medicine.”

—JAMES EVANS, UNIVERSITY OF NORTH CAROLINA,
Evaluation of Genomic Applications in Practice and Prevention

- CDC-funded initiative, with steering committee members 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.egapppreviews.org
EGAPP 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
- 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
Analytic framework

1. Adults with non-psychotic depression entering therapy with SSRIs
2. CYP450 genotype
   - Incorrect genotype assignment
3a. Metabolizer status (phenotype)
   - Predicted drug efficacy
   - Predicted risk for adverse drug reactions
3b. Treatment decisions
   - Improved outcomes:
     - Symptoms of depression
     - Shorter time to response
     - Fewer drug reactions
3c. Harms of subsequent management options
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?
Comparative effectiveness, marginal costs 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?
Recommendations from the EGAPP Working Group:
testing for cytochrome P450 polymorphisms in
adults with nonpsychotic depression treated with
selective serotonin reuptake inhibitors

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
Evidence is insufficient to recommend for or against UG1A1 genotyping in CRC patients to be treated with irinotecan with the intent of lowering the dose to avoid severe drug reactions

Evidence is adequate to recommend against routine testing for Factor V Leiden (FVL) and/or prothrombin 20210G>A (PT) in adults with idiopathic venous thromboembolism (VTE)
Completed recommendations

- Evidence is insufficient evidence to recommend testing for the 9p21 genetic variant or 57 other variants in 28 genes to assess risk for cardiovascular disease (CVD) in the general population; the magnitude of net health benefit from use of any of these tests alone or in combination is negligible; clinical use is discouraged unless further evidence supports improved clinical outcomes
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>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bins:</strong></td>
<td><strong>Bin 1</strong>&lt;br&gt;Medically actionable incidental information</td>
<td><strong>Bin 2A</strong>&lt;br&gt;Low risk incidental information</td>
<td><strong>Bin 2B</strong>&lt;br&gt;Medium risk incidental information</td>
</tr>
<tr>
<td><strong>Genes</strong></td>
<td><strong>BRCA1/2</strong>&lt;br&gt;<strong>MLH1, MSH2</strong>&lt;br&gt;<strong>FBN1</strong>&lt;br&gt;<strong>NF1</strong></td>
<td><strong>PGx variants and common risk SNPs</strong></td>
<td><strong>APOE</strong>&lt;br&gt;Carrier status for recessive Mendelian disorders</td>
</tr>
<tr>
<td><strong>Examples:</strong></td>
<td>10s (eventually 100s – 1000s)</td>
<td>1000s</td>
<td>10s</td>
</tr>
<tr>
<td><strong>Estimated number of genes/loci:</strong></td>
<td>10s</td>
<td><strong>Bin 3</strong></td>
<td>All other loci</td>
</tr>
</tbody>
</table>

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| Alleles that would be reportable (YES) or not reportable (NO) in a clinical context |
|---|---|---|---|---|---|
| **Variants** | **Known deleterious** | **Presumed deleterious** | **VUS** | **Presumed benign** | **Known benign** |
| N/A | N/A | **YES** | N/A | **YES** | **YES** |
| **YES** | N/A | N/A | **YES** | N/A | **YES** |
| **NO** | N/A | N/A | **NO** | N/A | **NO** |

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--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)
Practicality of EGAPP methods in WGS and binning

- Assessing clinical utility through systematic evidence review when evidence is available is expensive and time consuming.
- Assessing clinical validity with association studies can produce significant biases.
- Assessing the lack of clinical validity and even more so, the lack of clinical utility is relatively easy (when data are lacking) so the “quick no” or Bin 3/tier 3 assignment should be quicker and less resource intensive.