Current approached for evaluating genetic variants for clinical use

EGAPP: Evaluating Genomic Applications in Practice and Prevention

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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

JAMA 2008

COMMENTARY

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

Kathryn A. Phillips, PhD

NEW TESTING TECHNOLOGIES—INCREASINGLY BASED on genomic information—are essential in the shift toward personalized medicine and molecular ta

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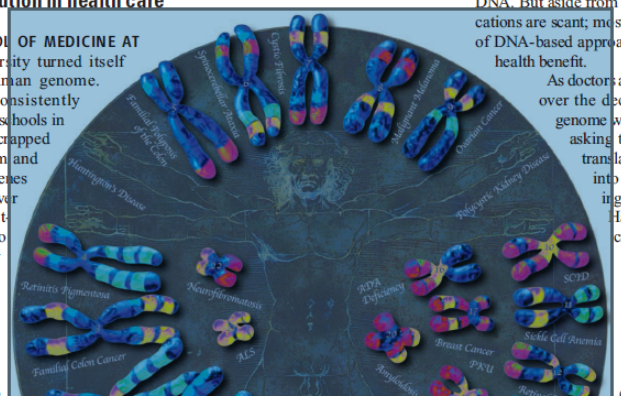
There is no consensus about optimal testing methods. Guidelines recommend using either immunohistochemistry, with indeterminate results confirmed by fluorescence in situ hybridization (FISH), or FISH to determine HER2 status.[1] Although FISH is a better predictor of response to

NEWSFOCUS | 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 biggest thing to



cal 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 narrowly 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?

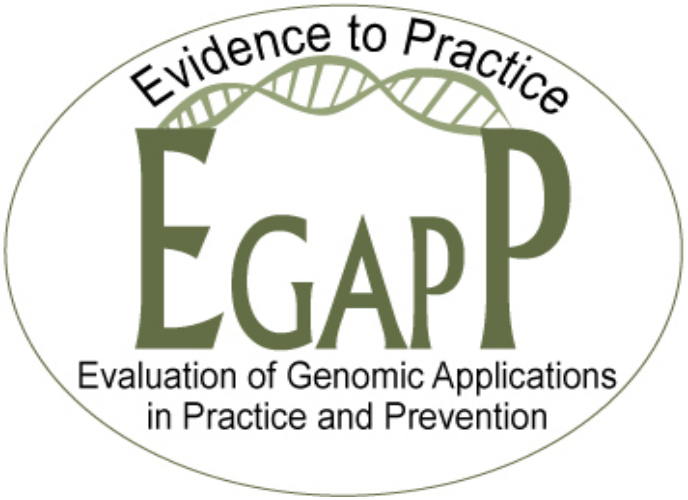
Such questions can elicit a sharp response from leaders in clinical genomics. Eric Topol, a pioneering researcher on DNA-related treatments in cardiovascular dis-

"We need to quit trying to push genetics into medicine."

—JAMES EVANS,
UNIVERSITY OF NORTH CAROLINA,

EGAPP

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.egappreviews.org

EGAPP approach

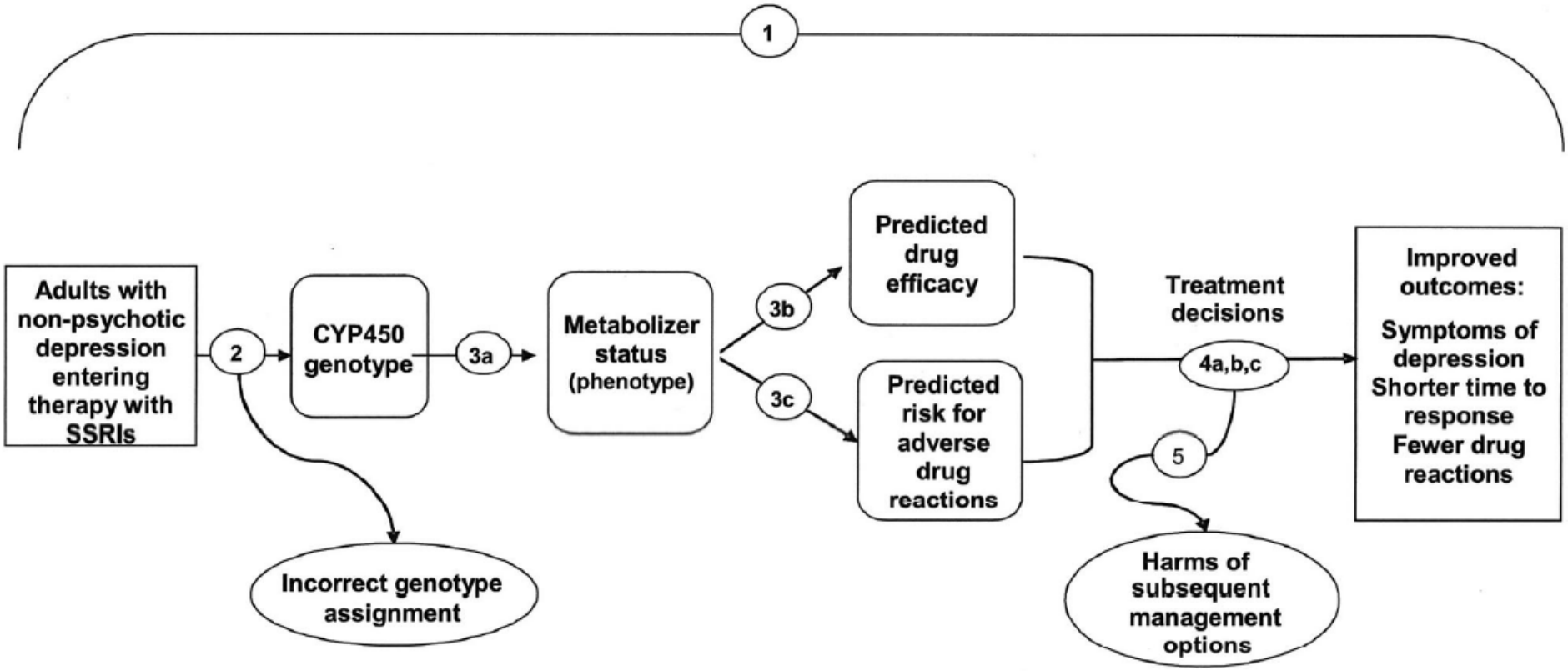
- Integrate knowledge and experience from existing processes
  - Genetic test assessment framework from ACCE
  - Assessment of quality of individual studies, adequacy of evidence, and level of certainty of net benefit (benefits minus harms) from USPSTF
  - Systematic evidence review and evidence syntheses 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

Genetics IN Medicine • Volume 11, Number 1, January 2009 *Methods of the EGAPP Working Group*



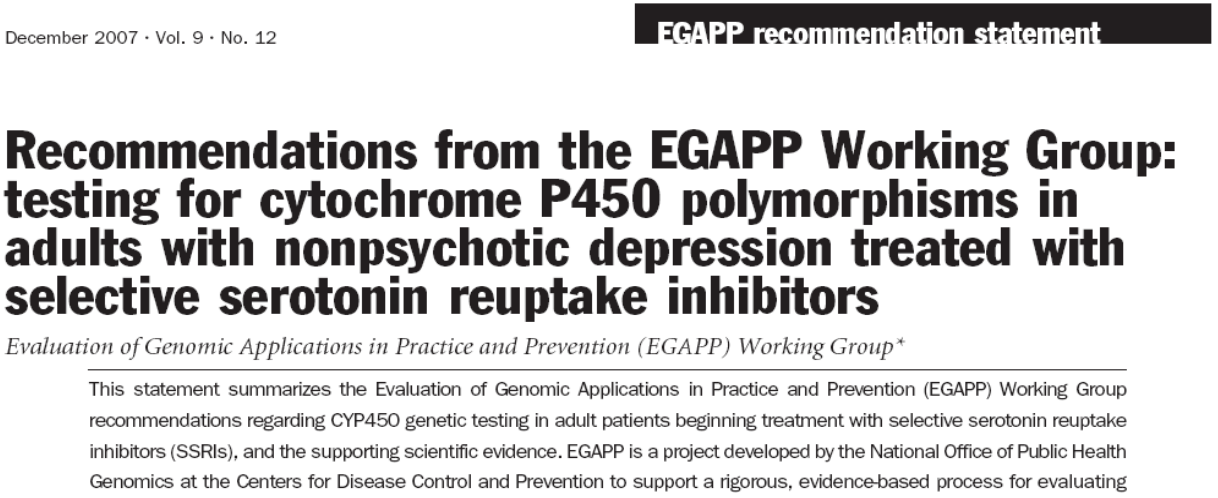
Key questions in analytic framework

- 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?

Completed recommendations



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EGAPP 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

Completed recommendations

- 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

	Criteria:	*Clinical Utility*	*Clinical Validity*			*Unknown Clinical Implications*
Genes	Bins:	**Bin 1 Medically actionable incidental information**	**Bin 2A Low risk incidental information**	**Bin 2B Medium risk incidental information**	**Bin 2C High risk incidental information**	**Bin 3**
	Examples:	*BRCA1/2* *MLH1, MSH2* *FBN1* *NF1*	PGx variants and common risk SNPs	*APOE* Carrier status for recessive Mendelian disorders	Huntington Prion diseases ALS (SOD1)	**All other loci**
	Estimated number of genes/loci:	10s	10s (eventually 100s – 1000s)	1000s	10s	~20,000
Alleles that would be reportable (YES) or not reportable (NO) in a clinical context						
Variants	Known deleterious	YES	YES/NO [1]	YES/NO [1]	YES/NO [1]	N/A [2]
	Presumed deleterious	YES	N/A [3]	YES/NO [1]	YES/NO [1]	NO [4]
	VUS	NO	N/A [3]	NO	NO	NO [4]
	Presumed benign	NO	N/A [3]	NO	NO	NO
	Known benign	NO	NO	NO	NO	NO

--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