# Translating Genome-Based Research for Health

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# What is the clinical utility of genetic testing?

*Scott D. Grosse, PhD[1], and Muin J. Khoury, MD, PhD[2]*

Evidence-based guidelines on the use of genetic tests in clinical practice require a systematic assessment of their usefulness, which, following a commonly used framework proposed in 1998 by a U.S. Task Force on Genetic Testing, is commonly referred to as clinical utility.[1] Clinical utility in its narrowest sense refers to the ability of a screening or diagnostic test to prevent or ameliorate adverse health outcomes such as mortality, morbidity, or disability through the adoption of efficacious treatments conditioned on test results.[2] A screening or diagnostic test alone does not have inherent utility; because it is the adoption of therapeutic or preventive interventions that influences health outcomes, the clinical utility of a test depends on effective access to appropriate interventions. This use is consistent with standard practice in evidence-based medicine, which focuses on objective measures of health status to evaluate interventions. Clinical utility can more broadly refer to any use of test results to inform clinical decision-making. Finally, in its broadest sense, clinical utility can refer to any outcomes considered important to individuals and families (e.g., reproductive decisions and psychosocial support). The field of genetic services, notably genetic counseling for Mendelian disorders, has emphasized the latter aspects of genetic testing.[2]

This commentary was prompted by a discussion at a workshop on the evaluation of genetic testing sponsored by the Centers for Disease Control and Prevention (CDC) in January 2005. The participants were a diverse group of experts in evidence-based medicine and genetics. The term "clinical utility" was familiar to many participants, and those who used the term were confident that they knew what it meant. However, there was no consensus as to what the term meant, with subgroups holding to different interpretations. This diversity of opinion led us to reflect on the meaning of the term and to review its previous uses. We came to realize that different definitions corresponded to different analytic and disciplinary or policy perspectives.

We concur with Scheuner and Rotter[3] that multiple perspectives should be considered in the evaluation of genetic testing, a conclusion that we had already reached. This commentary is a first response to their recent editorial. Only by making different perspectives explicit is it possible to reach agreement on the key endpoints to use in evaluating genetic testing for different audiences and purposes. Although different groups will not necessarily agree on which endpoints are most important, which involves value judgments and priorities, we hope that we can contribute to the clarification of these differences of opinion. The utility of genetic testing has different dimensions (public health, clinical, personal, and social), and the term "clinical utility" may be too limiting.

In this commentary, we review the evolution of the concept of clinical utility of biochemical or molecular testing for genotypic variations associated with risk of disease. Potential health-related applications include screening, diagnostic, and carrier testing for single-gene disorders, testing of multiple loci to construct disease susceptibility risk profiles, and pharmacogenomic testing to predict drug–genome interactions. Most applications to date fall under the single-gene category, but more are expected for common diseases with complex genetic contributions and gene–environment interactions. We do not consider non–health-related uses of genotyping, such as testing for physical traits such as athletic ability.[4]

## THE EVOLUTION OF THE CONCEPT OF CLINICAL UTILITY OF GENETIC TESTING

In 1997, the National Institutes of Health–Department of Energy Task Force on Genetic Testing proposed three criteria for the evaluation of genetic tests: analytic validity, clinical validity, and clinical utility.[1] By clinical utility, the report referred to "the balance of benefits to risks": "Before a genetic test can be generally accepted in clinical practice, data must be collected to demonstrate the benefits and risks that accrue from both positive and negative results."[1] In enumerating potential benefits and risks, the Task Force explicitly included social and psychologic benefits and burdens or harms of genetic information, such as the ability to avoid the conception of an affected child, reduction of uncertainty, increase in anxiety or fear of discrimination, and complacency from negative test results that can result in unhealthful behaviors. That is, an assessment of the ethical, legal, and social implications (ELSI) of a genetic test was explicitly considered as an aspect of clinical utility.

The report of the Task Force on Genetic Testing[1] led to the chartering in 1998 of a Secretary's Advisory Committee on Genetic Testing. In a report that called for enhanced federal oversight of genetic testing, the Secretary's Advisory Committee on Genetic Testing followed the Task Force in stating: "Clinical utility takes into account the impact and usefulness of the test results to the individual, the family, and society. The benefits and risks to be considered include the psychological,

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SCIENCE AND SOCIETY

# Ensuring the appropriate use of genetic tests

*Wylie Burke and Ron L. Zimmern*

Abstract | Ensuring the correct use of genetic tests is an important challenge for health-policy makers. Many new genetic tests will identify susceptibility to common diseases or adverse drug responses. Some will lead to new prevention opportunities, but others will have minimal clinical value. Statutory regulation alone cannot guarantee appropriate use. Other strategies, including resource allocation and matters related to clinical governance — such as practice-guideline development and health-provider education — are also important.

As a consequence of the completion of the Human Genome Project, an increasing number of genetic tests are becoming available to clinicians. New genetic tests will increasingly address clinical questions relevant to mainstream clinical practice, such as genetic susceptibility to common diseases and individual variation in drug response. Although some tests will provide effective new health-care alternatives, others will probably fall short of their promise, or entail substantial costs or risks. Defining and implementing genetic testing protocols that have a high chance of providing benefit, while avoiding questionable uses, represents an important health-policy challenge.

The promise of genetic testing — with its emphasis on 'PERSONALIZED MEDICINE' (see Glossary) and improved disease prevention — is intuitively appealing, and has been widely touted[1,2]. Genetic tests have traditionally been used to identify rare genetic conditions, but many new tests will identify relatively common gene variants that represent a new class of risk factors. With a large potential market for such tests, commercial incentives will have an important role in test development. Policy makers therefore have good reason to be wary of a technological imperative that might lead to the wide adoption of genetic tests without a considered assessment of the pros and cons.

There are several strategies for guiding the appropriate use of new medical technology; including evaluation procedures to define test properties, statutory regulation, decisions about the use of health-care resources, practice guidelines and health-provider education (FIG. 1). Here, we consider the application of these strategies to genetic testing.

## The challenge of genetic testing

Given the diverse clinical applications of genetic tests, determining appropriate use can be challenging (TABLE 1). For example, a test used to diagnose a rare genetic condition might also be used to predict its occurrence in asymptomatic family members, detect carriers for the condition or aid in prenatal diagnosis. Testing can be done in the absence of effective treatment to provide a prognosis or determine reproductive risk. Conversely, some tests are done primarily to guide treatment. Newborn screening, for example, is done to identify newborns with genetic disorders that require rapid initiation of treatment, such as PHENYLKETONURIA (see also Online links box). However ANALYTIC VALIDITY, CLINICAL UTILITY and CLINICAL VALIDITY are important properties to be considered for all genetic tests[3,4].

The assessment of clinical utility poses particular challenges for genetic tests that assess drug response or susceptibility to common diseases. In contrast to tests for single-gene disorders, these tests have limited predictive value. For example, factor V Leiden, a gene variant of the factor V gene, confers an increased risk of venous thrombosis[5]. However, a population-based study indicates that the cumulative risk by the age of 80 is only about 12% (REF. 6). Other risk factors, including other gene variants and non-genetic factors such as cigarette smoking, immobility, pregnancy, surgery and oral contraception, influence whether venous thrombosis will occur in a person with factor V Leiden. Importantly, most cases of venous thrombosis occur in people without factor V Leiden.

For tests of this kind, a stringent approach to clinical utility would recommend that the test be used only when effective interventions are available to improve the health outcome of people with the gene variant. Without effective therapy, testing could result in adverse labelling of an individual as genetically susceptible, without any commensurate health benefit; and could also lead to the use of unproven therapy with its associated risks. Moreover, the resources used in such tests could be used for other health interventions with beneficial outcomes. However, this perspective contrasts with the emphasis that medical genetics has traditionally placed on the value of knowledge about risk.

Disagreements can also occur about the evidence that is needed to document health benefit. For example, when is a randomized controlled trial necessary to prove a health-outcome benefit, versus less definitive observational data? Similarly, to what extent should tests be used as a means to motivate healthy behaviour? Many genetic tests can identify gene variants that increase the risk of heart disease; for example, apolipoprotein E4 (apoE4)

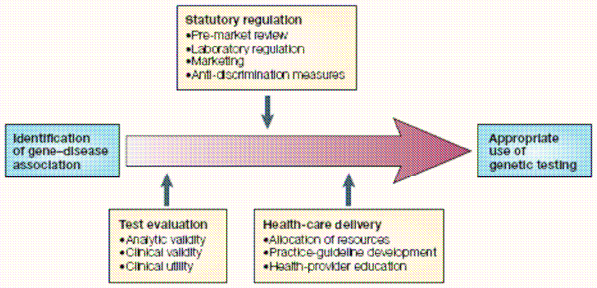


Figure 1 | **The discovery of a gene–disease association lays the groundwork for the development of a genetic test.** Technical evaluation is needed to define the test's properties. Both statutory regulation and mechanisms related to funding, practice-guideline development and health-provider education contribute to ensuring appropriate test use.

# Defining The Balance Of Risk And Benefit In The Era Of Genomics And Proteomics

The new world of personalized medicine demands that a rational approach to balancing risks and benefits be developed immediately.

by Robert M. Califf

**ABSTRACT:** The ability to measure the function of genes and proteins has spawned the construct of personalized medicine, in which patients' own risks and preferences are used to choose diagnostic and therapeutic strategies. The complexity of clinical data required to guide personalized medicine calls for improvements in our system of clinical research, including (1) overhauling it to produce networks that can do adequate-size pragmatic trials; (2) synchronization of regulatory and payment systems to encourage adequate studies; and (3) an investment in education of providers and patients to improve the understanding of the probabilistic predictions forming the basis of personalized medicine.

Health care is caught between two unremitting forces: a growing array of new technologies with associated expectations about effects on life expectancy and freedom from disability, and the constantly increasing cost of delivering these technologies.[1] Nobody wants to ration highly effective technology as a means of controlling costs. The preferred approach is to refrain from using ineffective technology, concentrating our spending on technology that improves longevity, quality of life, or productivity, coupled with a delivery system that maximizes the benefit and minimizes the risk to patients. As methods of measuring the benefit and risk of therapeutics have improved, the argument has shifted to a consideration of how the therapy's marginal benefit/risk balance relates to its cost relative to other alternatives.

The concept of personalized, prospective medicine improves the potential for successful, sophisticated evaluation of the balance of risk and benefit because it embodies the belief that technology is not simply effective or ineffective, but that it is likely to be more effective in some people and less effective or even harmful in others.[2] In theory, the attributes of technology can be tailored to the needs of the individual.[3] The anticipated effect of personalized medicine also fits with the in-

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# The Intersection Of Biotechnology And Pharmacogenomics: Health Policy Implications

The move toward greater personalization of medicine might conflict with lowering health spending and expanding access to care.

by Kathryn A. Phillips

**ABSTRACT:** Increasing knowledge of the genetic basis of disease is changing the landscape of health care. Two critical aspects are growth in biotechnology and growth in personalized health care, particularly targeting medicines based on genetic information (pharmacogenomics). This paper provides an overview of the health policy implications of the integration of biotechnology and pharmacogenomics. I examine four factors that determine whether relevant technologies will be successfully adopted, using case studies for illustration. Key policy challenges include determining the appropriate role of policy in (1) providing incentives to develop socially beneficial interventions and (2) facilitating development of the evidence base. [*Health Affairs* 25, no. 5 (2006): 1271–1280; 10.1377/hlthaff.25.5.1271]

OUR INCREASING KNOWLEDGE OF THE GENETIC BASIS of disease is changing the landscape of health care in multiple ways.[1] The shift that is under way has important implications across the board—for patients, providers, industry, insurers, and regulatory agencies. Two critical aspects of this shift are (1) growth in biotechnology applications in health care and (2) the move toward personalized health care, particularly medicines based on genetic information (pharmacogenomics, or PGx).

The biotech and PGx sectors are separate but overlapping. This paper focuses only on the overlap. Surprisingly, the link between biotech, PGx, and health policy has been relatively ignored in the literature; for example, a Medline search found no papers covering all three subjects. There have also been relatively few papers on biotech and health policy.[2]

The overlap of biotech and PGx is a relatively small piece of the market; how-

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# 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 for evidence could slow the integration of genomics into practice and present disincentives for investing in research and development. Also, variable coverage and reimbursement policies can lead to differential access to technology, exacerbating health disparities. There is an urgent need for a collaborative process for appropriate transition of genomic discoveries from research to practice. [*Health Affairs* 27, no. 6 (2008): 1600–1611; 10.1377/hlthaff.27.6.1600]

WITH ACCELERATING DISCOVERIES about the human genome and its role in health and disease, expectations of a new era of personalized health care and disease prevention are mounting. Several years after the completion of the Human Genome Project, genomewide association studies are uncovering genetic risk factors for common diseases of public health significance.[1] Genomic technology has also allowed the sequencing of the entire genome of selected individuals.[2] The stage is set for an accelerated pace of integration of genomics into medicine, as predicted.[3]

Undoubtedly, major progress will continue in technology development and our understanding of genetic variations, their interactions, and products.[4] The number of genetic tests used in clinical practice will increase.[5] Unfortunately, there is a mismatch between reality and expectation, related to both the quantity and the quality of evidence for genomic medicine. For example, the discovery of variants

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# A public health approach to pharmacogenomics and gene-based diagnostic tests

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While the human genome project is likely to lead to fundamental changes in our understanding of disease causation and our ability to screen for disease predisposition and treatment responsiveness, the current healthcare system is not properly aligned to ensure the proper use of these advances. As the pace of genetic technology development increases and new pharmacogenetic drugs and gene-based diagnostic tests increasingly impact providers, patients, health plans, payers and employers, it will be crucial to develop an evidence-based framework by which to evaluate these new tests and treatments. In order to increase the level of evidence available and allow for informed decisions in the face of strong marketing and advocacy forces, the authors suggest the development of one (or more) large clinical networks with the purpose of systematically evaluating the clinical effectiveness of new genomic applications, including pharmaceuticals and gene-based diagnostic tests, in 'real world' settings.

Keywords: clinical effectiveness, diagnostic tests, evidence-based medicine, observational studies, networks, pharmacogenomics, randomized clinical trials

Future Medicine

The completion of the human genome project promises fundamental changes in our understanding of disease causation and treatment, and our ability to screen for disease predisposition and treatment responsiveness [1,2]. Pharmacogenomics has the potential to improve drug discovery and development, as well as improve drug safety and effectiveness [3–5].

However, past performance in evaluating the safety and efficacy of drugs and in ensuring the proper use of screening and diagnostic tests in the USA has not been optimal, and should cause us to pause and consider the reasons for this current state of affairs [6–8]. The recent controversies over mammography screening, postmenopausal hormone therapy, and cyclooxygenase-2 (COX2) inhibitors have pointed to the need to substantially increase the level of evidence available to policy makers, providers and patients, in order to allow informed decisions in the face of strong marketing and advocacy forces. In the current biomedical research and marketing climate, there may be little incentive to perform head-to-head comparisons of new drugs with other medications, to compare new diagnostics with older ones or the current standard of care [9,10], and pertinent to genomics, assess whether or not drugs may have differential safety and effectiveness parameters for individuals with different genetic backgrounds. As a result, healthcare purchases, providers, physicians and patients often have far too little data regarding the utility or cost effectiveness of new therapeutics or tests [11,12]. Even when new treatments or diagnostics are shown to be beneficial, there is little agreement and few standards about how best to deliver these new advances to the patient, or how to decide when to adopt them in the delivery system.

In a recent editorial, Califf highlighted how the current system for approval and oversight of medical products at the US FDA – including pharmaceuticals and diagnostic tests – is antiquated [13], and is one where health outcomes research has taken a backseat to research that remains almost exclusively focused on the biologic function of medical products. The current regulatory environment for evidence collected regarding drug safety and efficacy and on diagnostic tests is primarily directed to that needed for licensure. The road to licensure for commercially developed pharmacogenetic-based drugs focuses first on compound discovery and then progresses through a series of trials that provide data on a drug's clinical response, safety and efficacy. For diagnostic tests, prelicensure evaluations focus primarily on the questions that inform analytical utility and sometimes clinical validity [13].

However, following licensure, as the drugs and tests become more widely used in the marketplace, important questions remain to be answered. Prelicensure studies rarely address issues of clinical effectiveness (as opposed to clinical efficacy), and don't gather information on the drug or test characteristics in 'real world' conditions [11,13]. These prelicensure clinical trials are typically restricted to highly selected groups of patients on monotherapy

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# Translating Genome-Based Research for Health

Goal: Personalized delivery of therapeutics that accounts for the genetic variation of the patient

Gene-based diagnostic tests are very powerful

- Have distinctive risk/benefit profiles
- May have unintended effects

Default for gene-based diagnostic tests and for pharmacogenetics should be:

- Randomized Clinical Trials (if/when feasible)
- Population-based observational studies

# Translating Genome-Based Research for Health

How do HMOs (~Kaiser) evaluate new genomic technologies?

1. Is there good evidence (RCT/obs) that it improves outcomes?
   - Gene testing for Her2 Neu status
   - Gene testing for Warfarin

2. Does it improve outcomes at a reasonable cost (money; resources; time)?
   - Abacavir hypersensitivity  NNS 25-30

ORIGINAL ARTICLE

# HLA-B*5701 Screening for Hypersensitivity to Abacavir

Simon Mallal, M.B., B.S., Elizabeth Phillips, M.D., Giampiero Carosi, M.D., Jean-Michel Molina, M.D., Cassy Workman, M.B., B.S., Janez Tomažič, M.D., Eva Jägel-Guedes, M.D., Sorin Rugina, M.D., Oleg Kozyrev, M.D., Juan Flores Cid, M.D., Phillip Hay, M.B., B.S., David Nolan, M.B., B.S., Sara Hughes, M.Sc., Arlene Hughes, Ph.D., Susanna Ryan, Ph.D., Nicholas Fitch, Ph.D., Daren Thorborn, Ph.D., and Alastair Benbow, M.B., B.S., for the PREDICT-1 Study Team*

## ABSTRACT

### BACKGROUND

Hypersensitivity reaction to abacavir is strongly associated with the presence of the HLA-B*5701 allele. This study was designed to establish the effectiveness of prospective HLA-B*5701 screening to prevent the hypersensitivity reaction to abacavir.

### METHODS

This double-blind, prospective, randomized study involved 1956 patients from 19 countries, who were infected with human immunodeficiency virus type 1 and who had not previously received abacavir. We randomly assigned patients to undergo prospective HLA-B*5701 screening, with exclusion of HLA-B*5701–positive patients from abacavir treatment (prospective-screening group), or to undergo a standard-of-care approach of abacavir use without prospective HLA-B*5701 screening (control group). All patients who started abacavir were observed for 6 weeks. To immunologically confirm, and enhance the specificity of, the clinical diagnosis of hypersensitivity reaction to abacavir, we performed epicutaneous patch testing with the use of abacavir.

### RESULTS

The prevalence of HLA-B*5701 was 5.6% (109 of 1956 patients). Of the patients receiving abacavir, 72% were men, 84% were white, and 18% had not previously received antiretroviral therapy. Screening eliminated immunologically confirmed hypersensitivity reaction (0% in the prospective-screening group vs. 2.7% in the control group, P<0.001), with a negative predictive value of 100% and a positive predictive value of 47.9%. Hypersensitivity reaction was clinically diagnosed in 93 patients, with a significantly lower incidence in the prospective-screening group (3.4%) than in the control group (7.8%) (P<0.001).

### CONCLUSIONS

HLA-B*5701 screening reduced the risk of hypersensitivity reaction to abacavir. In predominantly white populations, similar to the one in this study, 94% of patients do not carry the HLA-B*5701 allele and are at low risk for hypersensitivity reaction to abacavir. Our results show that a pharmacogenetic test can be used to prevent a specific toxic effect of a drug. (ClinicalTrials.gov number, NCT00340080.)

From Royal Perth Hospital and Murdoch University — both in Perth, Australia (S.M., E.P., D.N.); Università degli Studi di Brescia, Brescia, Italy (G.C.); Hôpital Saint Louis, Paris (J.-M.M.); AIDS Research Initiative, Darlinghurst, Australia (C.W.); University Medical Center Ljubljana, Ljubljana, Slovenia (J.T.); HIV Research and Clinical Care Center Munich, Munich, Germany (E.J.-G.); Infectioase Constanta, Bucharest, Romania (S.R.); Volgograd Regional Center for AIDS, Volgograd, Russia (O.K.); Hospital Arnau de Vilanova, Valencia, Spain (J.F.C.); St. George's Hospital (P.H.) and MediTech Media (S.R.) — both in London; GlaxoSmithKline, Greenford, United Kingdom (S.H.); GlaxoSmithKline, Research Triangle Park, NC (A.H.); and GlaxoSmithKline, Brentford, United Kingdom (N.F., D.T., A.B.). Address reprint requests to Dr. Mallal at the Institute for Immunology and Infectious Diseases, Murdoch University, South St., Murdoch, WA 6150, Australia, or at s.mallal@murdoch.edu.au.

*Members of the Prospective Randomized Evaluation of DNA Screening in a Clinical Trial (PREDICT-1) study team are listed in the Appendix.

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# Major challenge:

- Lack of evidence/data to support integrating new genetic tests/technologies or applying them to old drugs

# Joint informal collaboration(s) with PGRN and AHRQ DEcIDE

Informal decision-making process decides which drug classes to study:

- Metformin
- Statins
- Asthma-related (beta-agonists; steroids)

Implicit and explicit determinations:

- Substantial morbidity/mortality (DM; CVD; Resp)
- Substantial cost-drivers
- Substantial number of exposed patients
- Recent advances in science ready to assess impact in population-based setting ('shovel-ready')

*Goal: To collect the evidence needed to decide whether to adopt testing into practice*

PGRN: Gene - discovery of polymorphisms influencing response

HMORN: What is role of gene in predicting response *in routine practice*

- Case-control study assessing role of polymorphisms in patients who do or do not respond to drug(s)
- Validation study
- Develop dosing and/or medication choice guidelines depending on genetic status (may require separate evidence gathering step)
- Randomized trial of gene-directed medication choice/dosing

# Example: Metformin

PGRN: Discovery of polymorphisms influencing response to metformin

HMORN: Case-control study
Cases = non-responders to metformin
Controls = responders to metformin

Exposure = polymorphisms

If study reveals strong association, then validation f/b RCT

- Arm 1: Testing for polymorphisms, with gene-guided choice of metformin or sulfonylureas
- versus
- Arm 2: Usual care

# Example: Asthma

PGRN: Discovery of polymorphisms influencing response to asthma medications

HMORN: Case-control study
Cases = non-responders to steroids/albuterol/MLK
Controls = responders to steroids/albuterol/MLK

Exposure = polymorphisms

If study reveals strong association, then validation f/b RCT

- Arm 1: Testing for polymorphisms, with gene-guided choice of steroids/albuturol/MLK
- versus
- Arm 2: Usual care

# Barriers

1. Research Infrastructure
2. Data systems
3. Mismatched incentives for licensure

## Barrier 1: Research Infrastructure

1. No formal research infrastructure with adequate funding for outcome studies of new genomic technologies. As a result, outcome studies have, to date, been bootstrapped onto discovery projects

# Barrier 2: Inadequate data systems

2. Data systems are lagging behind

   - Most ICD-9 codes/CPT codes are inadequate to task of:

     1. (efficiently) Identifying patients tested for Her2Neu, Oncotype etc status

     2. (efficiently) Identifying her2neu results

     3. Can't assess if test is done appropriately, or whether rx (herceptin) is being used appropriately

     4. In these situations, observational data inadequate for studies of test effectiveness, relegating us to RCTs of new genetic tests

# Barrier 3: Mismatched incentives

1. For ***licensed*** tests – decision to integrate into practice will hinge on demonstrating improved outcomes in large, population based settings

2. For some tests (e.g. oncotype; warfarin) RCTs may be feasible and justifiable

   For others – clinical trials not feasible. Observational data may suffice, but may only be available post-licensure. Regardless, no funding agency likely to evaluate commercial product.

3. No regulatory incentive for companies (RCTs or Observational)

   Without fundamental changes, may lead to repeated examples of poor update of potentially valuable technologies (e.g. amplichip)


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- May have unintended effects

Default for gene-based diagnostic tests and for pharmacogenetics should be:

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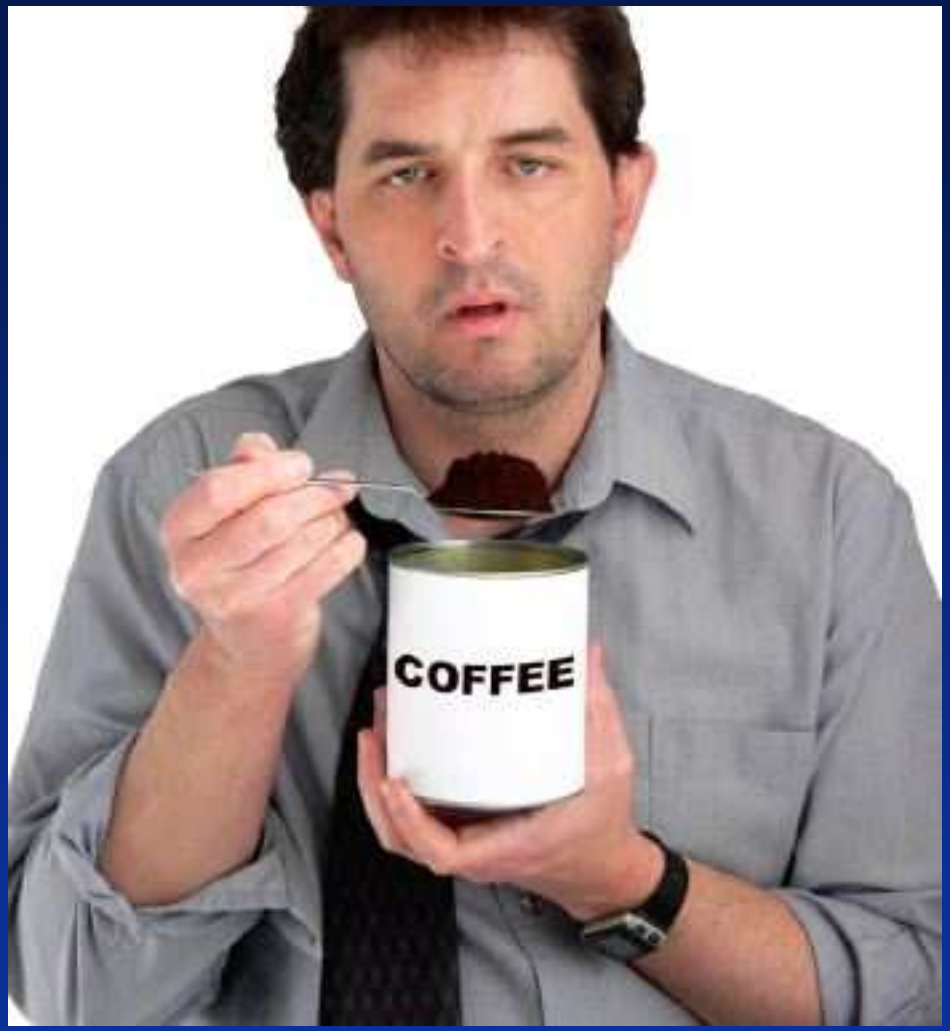
- Population-based observational studies

Should they, similar to pharmaceuticals, need proof of clinical utility/ improved outcomes as a requirement linked to licensure?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