



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.

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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and without other significant comorbidities; however, following licensure these same medications are frequently used on populations that differ markedly in terms of age, race, comorbid conditions and concomitant use of other medications. How the drug performs in these conditions – whether it improves clinical outcomes, whether it affects quality of life indicators such as improved and/or more rapid control of symptoms, or whether it improves the avoidance of medication – adverse events – is often simply not known. Additionally, as with all new medication or technology, it is necessary to establish whether the drug or test performs better than the usual ‘standard of care’; whether it reduces or increases costs of care, and whether there are any untoward or unanticipated downstream outcomes or effects of the new test once busy clinicians try to implement these findings in practice. While preclicensure studies can answer some of these questions, typically the extent of the data that is gathered is far from complete.

Hence, the extent of the evidence and data gathered prior to licensure does not provide sufficient information on the effectiveness of medications or diagnostic tests when utilized in the general population [14,15]. Although there is substantial benefit that comes from the data on clinical efficacy arising from preclicensure trials, the public health interest in pharmacoepidemiology and tests is focused instead on the real world effectiveness of clinically applied drug and test development, and in monitoring its applications and health outcomes in a diverse range of environments. As the pace of genetic technology development is increasing, and as 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 to evaluate these new tests and treatments [16–19].

The purpose of this present paper is to outline a public health approach to systematically integrate genomics into an evidence-based clinical and public health practice. To accomplish this, we need to ask four questions:

- What type of research is required in order to collect the evidence needed to guide clinical decisions and public health policy?
- What processes are needed to synthesize this research and in turn set priorities for further research?
- How can the synthesis of this research be best integrated into policy and the delivery of health services?

- What surveillance activities should be planned in order to assess the ongoing performance of implementation into clinical practice?

A schematic of this process is shown in Figure 1, illustrating the need for studies that collect evidence of effectiveness; synthesis of information; studies that assess the best way to integrate the evidence into clinical practice; and finally a system that can provide surveillance of implementation practices and ensure the proper utilization of the diagnostic tests.

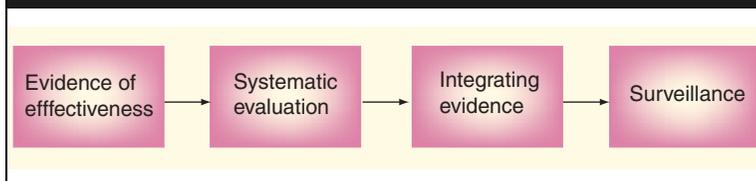
Evidence of effectiveness

A recently introduced pharmacogenomic test for cytochrome P450 (*CYP*) genetic variants may provide a useful example. Metabolism of many drugs administered today occurs primarily in the liver through oxidative metabolism by a complex series of *CYP* enzymes. Drug interactions and adverse effects involving *CYP* are common and usually result from enzyme inhibition or induction. The effects of enzyme induction or inhibition are difficult to predict as they are dependent on drug half-lives, the rate of enzyme production and individual genetic variations [20]. Genetic differences are a major reason one patient might be susceptible to interactions or adverse effects when another may not [21].

The *CYP* genotyping test is the first DNA microarray-based pharmacogenomic test to be made available for use in the USA [101]. The test provides information on enzyme activity of the *CYP2D6* and *CYP2C19* genes, which play particularly important roles in the metabolism of a large number of widely-prescribed medications. Variations in these genes can cause a patient to metabolize certain drugs more quickly or more slowly than typical, or, in some cases, not at all [101]. Other genes, such as the *N*-acetyltransferase (*NAT*) isoenzyme, are also involved with drug metabolism but are not covered by the *CYP* test.

It is anticipated that the use of *CYP* testing in the clinical setting may enable physicians to identify individuals who are either slow or rapid metabolizers, and who might therefore be at increased risk for toxicity or nonresponse, respectively. However, as no clinical trials or other types of studies have actually assessed the best way to employ this test in practice, it is currently not clear how this information could allow physicians to employ a ‘personalized medicine’ approach to their individual patients, and use the individualized tests results to select a drug or

Figure 1. A proposed public health approach to the real world effectiveness of pharmacogenomics and gene-based diagnostic tests.



dosage for each particular patient. Also, the cost of this type of pharmacogenomic test may be substantial, and health plans and other payers will want to gather information on the incremental benefit that this test affords above and beyond the current standard of care. Evidence on the effectiveness and cost-effectiveness of the *CYP* testing could potentially be gathered from either observational or clinical trial data.

Observational data, from case-control or cohort studies, or other similar designs, have been frequently used to address questions about test effectiveness, particularly in studies that are centered within large, well-defined populations. In order to specifically provide this specialized type of clinical effectiveness data, a cohort study of the *CYP* testing could be devised whereby the clinical outcomes of patients whose physicians utilize the test would be compared with those whose physicians do not use the test. In this way, one could examine how the test influences outcomes among a wide range of patients on medications, such as antidepressants, antipsychotics and/or β -blockers.

A substantial advantage of these types of observational studies is that the data are often readily available from administrative files or other similar types of sources, reducing the time and cost compared with a large clinical trial [22]. However, perhaps the most serious limitation to these studies is that the test interpretation is limited by the amount and extent of information available on other characteristics that also affect treatment decisions or influence outcomes [23]. For example, if a study was performed in a clinical practice where the test was used preferentially among those patients at highest risk (either for poor treatment outcome or medication-related adverse events) or, in another case, if the physicians who incorporated the test into their practice differed substantially from those who do not in terms of their overall quality of care, then this type of observational study of clinical outcomes associated with use of this test could be substantially biased.

An even more compelling type of evidence would come from randomized clinical trials, which could provide the strongest evidence into the effectiveness of gene-based diagnostic tests. In the above example, a randomized clinical trial would ensure the relatively even distribution of observed and unobserved characteristics which could otherwise influence the decision to utilize the *CYP* test, or of characteristics independently related to clinical outcomes. Another advantage to randomized trials is that they allow for flexibility in enrollment, so that enrollment can be enriched based on gene status. For example, in the observational study of *CYP* test described above, the power of the study would be limited in its ability to study test effectiveness among persons with relatively rare polymorphisms of the *CYP* pathway. However, in a randomized trial, one could test potential study subjects for genotype and, where needed, enrich participation specifically for the rare and underpopulated strata, thereby increasing the study's ability to assess differential treatment effects by genotype strata. As before, the rate of good or poor outcomes following treatment would still be compared between different genotype strata, but with greater power due to larger samples in each strata.

Another type of study design – the practical clinical trial – promises to help address the limitations of both observational studies and traditional randomized clinical trials [14]. Large practical clinical trials focus on recruiting a large, diverse population of participants, cover a wide range of different practice settings, and collect information on clinical effectiveness and health outcomes. These studies contrast to usual clinical trials of efficacy in that they contribute information on costs, a wide range of morbidity and mortality. As such they are particularly valuable for policy and decision makers in clinical practice.

Ultimately, a wide range of observational studies and clinical trials will likely be necessary in order to collect the most complete picture possible of genomic test effectiveness. It is unlikely that any single study, or even set of studies, will provide all the necessary evidence pertaining to effectiveness. However, what is increasingly clear is the need for a systematic approach for synthesizing the evidence that comes from these different types of studies.

Evidence synthesis

Currently, much of the new research into complex diseases focuses on examining the interaction between genetic predisposition and environmental

exposures; however, the advent of genomic tools has caused the field of epidemiology to re-evaluate how to assess the results of single studies. As Ioannidis as pointed out, the identification of genetic determinants for complex, multigenic diseases has been severely hampered by small studies, publication and reporting biases, and a lack of common reporting standards. Ioannidis and others have called for a network of networks in order to standardize the data collection and analysis among investigators collecting data for human genome epidemiology research [24]. Bracken also noted the explosion in the technological capacity of genetic epidemiology studies, with investigations routinely assessing the association between tens of thousands of polymorphisms and complex diseases [25]. Because of this challenge to replicating findings in studies of genomic epidemiology, he called for an evidence-based collaborative model that would facilitate the systematic review of gene–disease associations.

In a similar vein, studies into what works and what doesn't work in healthcare has faced the challenge of interpreting evidence from widely disparate study designs, often on small populations, using nonstandardized outcome measures, and in different healthcare settings. In response, the evidence-based practice center program was established by the Agency for Healthcare Research and Quality (AHRQ) to develop systematic reviews of the evidence on questions of healthcare importance [15]. Building upon this paradigm, the Office of Genomics and Disease Prevention at the Centers for Disease Control and Prevention recognized the need to develop a more systematic means to evaluate the evidence supporting the effectiveness of genomic applications in practice. A model project, known as the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) was established in order to help coordinate systematic reviews of genomic applications as they transition from research into clinical and public health practice [102]. This project relies on an independent, non-Federal working group composed of experts in healthcare, public health, epidemiology and evidence-based medicine to prioritize topics for review and to oversee an expert systematic review of evidence reports focusing on the application of genomic tests in the clinical settings. While still in its early stages, one explicit goal of this group will be to highlight gaps in knowledge, and to clarify what type of further research is needed. In particular, it is likely that many of the early reviews of genomic

applications (such as for *CYP* testing) will identify substantial gaps in our knowledge of how gene-based diagnostic tests improve patient outcomes. Hence, one priority of EGAPP will be to recommend an evidence-based approach toward gathering this information in a format and structure that can be systematically evaluated.

Studies for integrating evidence into practice

Once sufficiently strong evidence has been gathered on how a new genomic-based application affects clinical outcomes, work is then needed on how to best integrate this evidence into practice. Historically, attempts to integrate knowledge into practice have relied on educational efforts, typically by healthcare providers or patients (for example, academic detailing directed toward private physicians using opinion leaders), or other methods that primarily targeted clinicians or patients. Other attempts to translate research into practice have focused on computerized decision support systems, audit and feedback, patient-mediated interventions, or some combination of these methods [26]. Often these practices were relatively expensive, had limited effectiveness, or their effectiveness waned once the intervention was curtailed. In response to this difficulty, there has been a recent move to more formally study the best ways of integrating evidence, and to actually use clinical trials or quasi-experimental designs in order to understand how to study the best way of translating research into practice [26–28].

With the promise of new genomic applications, it will be important to carefully evaluate how best to integrate these new gene-based diagnostic tests into clinical care. As one example, using the case of the *CYP* test again, pilot studies to evaluate the most efficient ways of implementing this test could be performed in a health plan that uses an electronic medical record (EMR) with prescribing capabilities. The study's objectives would not be to evaluate whether using the test improves care or reduces adverse events, but would rather be to see how best to utilize the test in the course of regular care. In this example, in one arm of a study, some clinics or practices would be randomized to follow routine or typical clinical practice, and ostensibly would incorporate testing as individual providers see fit. In the other study arm, an intervention would be tied to prompts triggered within an EMR. Practices or clinics using the EMR for prescribing medications

would be prompted to use the test whenever a relevant medication was initially being prescribed. Such prompting could be tied to a standardized reporting format for test results along with interpretations and suggestions for medication-specific dosing adjustments. One benefit of these types of studies is the insight they provide on the ability of both the diagnostic test and the healthcare system to improve clinical outcomes, since both need to function properly for a patient to benefit.

Surveillance

Following evidence generation, synthesis and integration, the final component of a public health approach to pharmacogenomics and gene-based tests comes under the scope of surveillance, and would focus on measuring and tracking health outcomes, quality measures and the ethical applications of gene-based diagnostic tests. As gene-based diagnostic tests become more widely utilized as part of the therapeutic landscape, federal, state and other regulatory agencies may have an interest in gaining the capacity for monitoring patterns of utilization rates in various subgroups of the population. One form of surveillance might be to assess the proportion of patients who are tested with the appropriate gene-based diagnostic test upon the initiation of certain therapies or to monitor its appropriate usage. Other surveillance might be performed to understand the patterns of test use among specific populations, such as those in underserved populations, those with chronic illnesses, or on Medicaid. In this same vein, systems should be put into place that would allow surveillance for whether gene-based diagnostic tests have unintended outcomes, such as loss of insurance, decreased access to (or reduced timeliness of) healthcare, and to understand whether the information is being transmitted to physicians and patients in a timely and understandable manner.

While such a system has not been discussed previously for pharmacogenomics or for gene-based diagnostic tests, this paradigm has already been well established at the Centers for Disease Control and Prevention (CDC), which carries out surveillance routinely. Much of these types of surveillance activities are condition specific, for example, on infectious diseases, unintentional injuries and sexually transmitted diseases. The CDC routinely collects information, for example, on vaccination practices in different parts of the country in order to monitor guideline adherence and to establish the reasons for

incomplete or inappropriate vaccination administration. The need for a system able to monitor proper application of gene-based diagnostic tests should be considered by public health agencies, especially in light of the many different societal forces that will influence the uptake of pharmacogenomic tests and gene-based diagnostic tests.

Developing a genomic applications in practice network for research & surveillance

It will be a large task to put together a network of research and surveillance in healthcare settings that can provide evidence collection, synthesis, integration efforts, and surveillance on genomic applications. In order to develop a systematic approach, there needs to be a structure for setting priorities, for identifying clinical investigators, patient populations, and funding partners. This is not necessarily a new idea: large and sophisticated clinical trial networks in cardiovascular medicine [29,30] and in pediatric oncology [30] have demonstrated both the means of accomplishing these goals and the substantial benefits and advances that emanate from such a collaboration [31].

There is no such network yet that focuses on the clinical or public health impacts of gene-based therapies and pharmacogenomic applications, although the need for one has been identified by many experts involved in various aspects of this field [3,4,13,32]. AHRQ has sponsored the development of the Developing Evidence to Inform Decisions about Effectiveness (DEcIDE) network, specifically to facilitate comparative effectiveness, safety and cost-effectiveness studies of therapies and health services within populations that are often excluded from randomized clinical trials, but who are the target of the therapies; however, there is little, if any, funding directed toward the study of genomic applications within this new and promising network.

Numerous diverse groups have a vested interest in ensuring that the discoveries that emanate from the Human Genome Project (HGP) are properly integrated into clinical medicine. Government agencies and biotechnology and pharmaceutical industries, healthcare plans, insurance companies, consumer advocacy groups, and providers and patients all depend on the creation of good evidence supporting the decision to use (or pay for the use) of genomic applications. However, the National Institutes

Highlights

- Pharmacogenomics has the potential to improve drug discovery and development, and improve drug safety and effectiveness.
- The past performance in the USA in evaluating the safety and efficacy of drugs and in ensuring the proper use of screening and diagnostic tests has been suboptimal and may inhibit the proper use of pharmacogenomic advances.
- Data gathered prior to licensure does not provide sufficient information on the effectiveness of medications or diagnostic tests when utilized in the general population.
- As 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 for which to evaluate these new tests and treatments.
- To successfully develop this evidence-based framework, we need to ask: what type of research is needed to guide clinical decisions and public health policy; how can we synthesize this research and in turn set priorities for further research; how can we integrate this research into policy and delivery of health services; and how can we continually assess the implementation of this evidence into practice?
- Both observational studies and clinical trials will likely be necessary in order to collect the most complete picture possible of genomic test effectiveness.
- A model project, known as Evaluation of Genomic Applications in Practice and Prevention has been formed by the Office of Genomics and Disease Prevention at the Centers for Disease Control and Prevention in order to help coordinate systematic reviews of genomic applications as they transition from research into clinical and public health practice.

of Health (NIH) is typically not involved in outcomes and clinical effectiveness research, except via disease- or organ-specific clinical trials networks mentioned before. Biotechnology and pharmaceutical companies have an obvious interest in seeing the widespread application of genomic-based technology, but might not fund studies that might show less than anticipated benefits, or benefits that are not cost-effective when viewed from a payer's perspective. Healthcare plans and insurance companies have not typically provided the funding for this type of research, although they are often active participants, providing either study populations or scientific expertise. The FDA has not yet asserted a regulatory requirement for new genomic applications, and some have argued that increased regulation might be counter-productive [33]. Nevertheless, the recent high-profile withdrawal of the rhesus rotavirus vaccine and COX2 inhibitors from the market demonstrate the clear need for such increased regulation, and the US FDA is increasingly inclined to require larger postmarketing studies of safety once pharmaceuticals are widely distributed after licensure. The infrastructure that is put into place to carry out these safety studies can, with careful planning, be used to also provide the framework with which to gather information on clinical effectiveness and outcomes of genomic applications.

Outlook

In their landmark article, Collins and others laid out a series of grand challenges for the medical community to meet in order to fully capture the promise of the HGP [1]. The six crosscutting elements that were included in these challenges included resources, technology development, computational biology, training, ethical, legal and social implications, and education. The purpose of this paper was to make a public health case for an additional aspect needed in order for many of these challenges to be met. Specifically, we need to create the necessary collaborative evaluation of genomic applications in practice network that will allow us to understand the clinical effectiveness of new genomic applications, including pharmaceuticals and gene-based diagnostic tests in 'real world' applications. Such a network must truly cut across organ systems, diseases and disciplines, and must allow the systematic collection of evidence, synthesis and integration of evidence, and surveillance that will be desperately needed by policy decision makers, regulators, clinicians and patients in order to fulfill the promise of the new, and also the as yet undiscovered, genomic advances in the 21st century.

Disclaimer

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

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