

## **The Genomic Applications in Practice and Prevention Network (GAPPNet)**

Muin J. Khoury (1), W. Greg Feero (2), Michele Reyes (1), Toby Citrin (3), Andrew Freedman (4), Debra Leonard (5), and the GAPPNet Planning Group.

Members of the GAPPNet Planning Group are: Wylie Burke (6), Ralph Coates (1), Robert Croyle (3), Karen Edwards (7), Sharon Kardia (2), Colleen McBride (2), Teri Manolio (2), Gurvaneet Randhawa (8), Rebekah S. Rasooly (9), Jeanette St. Pierre (1), Sharon F. Terry (10),

1. National Office of Public Health Genomics, Centers for Disease Control and Prevention, Atlanta, Georgia
2. National Human Genome Research Institute, National Institutes of Health, Bethesda, Maryland
3. Center for Community and Public Health Genomics, University of Michigan, Ann Arbor, Michigan
4. Division of Cancer Control and Population Sciences, National Cancer Institute, National Institutes of Health, Bethesda, Maryland
5. Cornell University, New York, New York
6. Center for Genomics and Healthcare Equality, University of Washington, Seattle, Washington
7. Center for Genomics and Public Health, University of Washington, Seattle, Washington
8. Agency for Healthcare Research Quality, Rockville, Maryland
9. National Institute for Diabetes, Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland
10. Genetic Alliance, Washington, District of Columbia

The report does not necessarily reflect the views and policies of the Department of Health and Human Services

Acknowledgements: The authors would like to thank the following individuals for comments on the paper: Elizabeth Gillanders, Dina Paltoo, Margaret Piper, Leah Sansbury and Daniela Seminara.

## Abstract

The authors describe the rationale and development of a new collaborative initiative, the Genomic Applications in Practice and Prevention Network (GAPPNet). The network convened by the Centers for Disease Control and Prevention and the National Institutes of Health includes multiple stakeholders from academia, government, health care, public health, industry and consumers. The premise of GAPPNet is that there is a large chasm between gene discoveries and their clinical validity and utility for successful applications in healthcare and disease prevention. This chasm is due to the lack of readily accessible information about the utility of most genomic applications and the lack of necessary knowledge by consumers and providers to implement what is known. The mission of GAPPNet is to accelerate and streamline the effective integration of validated genomic knowledge into the practice of medicine and public health in the United States, by empowering and sponsoring research, evaluating research findings, and disseminating high quality information on candidate genomic applications in practice and prevention. GAPPNet will develop a process that links ongoing collection of information on candidate genomic applications to 4 crucial domains: 1) knowledge synthesis and dissemination for new and existing technologies, and the identification of knowledge gaps, 2) a robust evidence-based recommendation development process, 3) translation research to evaluate validity, utility and impact in the real world and how to disseminate and implement recommended genomic applications , and 4) programs to enhance practice, education and surveillance.

Key words: decision support, genomics, information, medicine, network, public health

The ongoing success of genome wide association studies (GWAS) in uncovering genetic risk factors for many common diseases has renewed expectations of a new era of health care, with personalized treatment, disease prevention and early detection (1-3). Concomitantly, there is a rising interest in understanding the benefits and harms of genome-based technologies in real world settings (4), developing evidence-based guidelines for the use of genomic applications (5), and using policy and legislation to prevent discrimination on the basis of genetic information (6).

More recently, genome-wide profiles have been developed and marketed directly to consumers (DTC), with the implicit if not explicit goal of providing information for improving health and preventing common diseases (7). The ready availability and complexity of these new tests could strain the ability of consumers and the health care delivery system to determine the true value of applying extensive quantities of genomic data to health management. Proponents of genome-wide profiles assert that these tests can empower and educate individuals about disease prevention and health promotion. Others are concerned that the use of these tests is based on an incomplete knowledge about the relationship between genetic variation and human diseases, and the lack of a full understanding of specific medical or lifestyle interventions that should be offered based on these test results (8). Questions also remain regarding the scope of individual genetic tests that should be included in genomic profiles, whether the underlying technologies are robust, and where the balance lies between potential benefits and harms (clinical utility) of these tests to individuals and populations (8, 9). Table 1 shows multidisciplinary research needed to evaluate the use of genome wide profiles for risk assessment and disease prevention.

The emergence of genome wide profile tests underscores the need for clinical validity and utility information for all genomic applications, including pharmacogenomics, screening, early detection and disease management. For example, the United States Preventive Services Task Force (USPSTF) has recommended against screening for hereditary hemochromatosis in the general population since the potential harms outweigh the benefits (10). A recent report found several limitations in the existing U.S.-based research and healthcare delivery infrastructure to create an evidence base of utilization and outcomes of gene-based applications (11). Overcoming these limitations would require coordinated efforts that span multiple disciplines including genomics, laboratory medicine, epidemiology, behavioral and social sciences, health services research and health information technology, as well as engaging multiple stakeholders such as patients, health care providers, payers, regulators, public health and research funding agencies.

This paper discusses the development of an open and cooperative means for building the evidence base for emerging technologies and to transition them to proven and widely accepted health interventions with multiple stakeholder groups including the public, health care providers, biotechnology firms, researchers, policy makers, public health institutions, as well as private and public insurers.

### **A hypothetical case study: need for evidence-based information**

To illustrate how a collaborative mechanism to develop, synthesize, and disseminate credible information could benefit various stakeholders, consider a hypothetical commercial genetic test proposed for use by healthcare providers – a panel of genetic markers to aid selection of drug choice and dosing for the management of type 2 diabetes. Currently, this type of test would probably emerge from data amassed by investigator-driven genome wide association studies, then packaged as a test by a laboratory or pharmaceutical company, and marketed to health care providers and consumers. At the time the test enters the market, minimal evidence might be available to stakeholders regarding the test’s analytic and clinical validity, and it is probable that no clinical utility would be available. Unfortunately, after the test reaches the market, there is little incentive, and a number of barriers, to conducting research that can answer questions regarding clinical utility. The hypothetical diabetes test could meet with substantial skepticism by researchers, provider groups, insurers, public health institutions and policymakers. This would limit its potential for reimbursement, uptake, and, ultimately, public health benefit. On the other hand, consumer interest in the test could also create a supply-demand chain that propels the test into clinical use before adequate evidence has been established.

A collaborative model for facilitating and coordinating the translation of genomic applications to health care could dramatically improve the process for all groups. Returning to the example of the hypothetical diabetes test, one can envision several key functions that a coordinated system for translation might provide. First, all stakeholders could benefit from an unbiased initial assessment of the proposed diabetes test after the assignment of intellectual property rights. Based on preliminary data, the assessment could define analytic

validity, clinical validity and potential clinical utility of the test to various stakeholders, and identify of gaps in the knowledge base required for downstream acceptance and/or reimbursement by the public, care providers, and insurers. This type of early pre-market assessment would permit stakeholders to develop priorities for funding, and potentially spur private investment in downstream studies required to bring the hypothetical test to market and widespread use. Second, all stakeholders could benefit from an enhanced means for communication among and within groups. A means to align priorities and coordinate translation efforts could substantially reduce duplicative spending and time delay, and create an “evidence match” between the evidence generation process and the priorities of insurers, health care providers and policy makers. Finally, all stakeholders could benefit from a structured means for coordinating evidence synthesis, dissemination, and educational efforts (for both health care providers and the public) in the immediate pre-market and post market phase of test development and deployment. Currently, even the most promising applications may not reach a wide audience due to a lack of effective migration of evidence into national health care guidelines and the inefficient application and uptake of those guidelines in the health care sector. Coordination of these activities is critical to realizing the benefit of any new technology, and has been recognized as a major stumbling point in the translational continuum (12, 13).

### **The Genomic Applications in Practice and Prevention Network (GAPPNet) Initiative**

We believe that the development and availability of reliable and updated information on genomic applications in health practice in the United States can be accelerated by a new

collaborative initiative (Table 2). At the heart of the initiative is the convening of individuals and organizations interested in translating high-impact, appropriately-validated genomic applications into practice and prevention. GAPPNet will include interested individuals and groups from academia, government, health care and public health professionals, behavioral and social scientists, health care payers and plans, policy makers, media, disease-specific organizations, business, the biotechnology and pharmaceutical industries, educators, and information technology developers. The *vision* of GAPPNet is to realize the promise of genomics (and related fields) in treating and preventing disease, improving health, and reducing health disparities. The *mission* of GAPPNet is to accelerate and streamline the effective integration of validated genomic knowledge into the practice of medicine and public health in the United States, by empowering and sponsoring research, evaluating research findings, and disseminating high quality information on candidate genomic applications in practice and prevention. The *premise* of GAPPNet is that there is a chasm between gene discoveries and their clinical validity and utility for successful applications in healthcare and disease prevention. This chasm is due to the lack of readily accessible information about the validity and utility of most genomic applications and the lack of necessary knowledge by consumers and providers to implement what is known. Therefore, there is an urgent *need* to: 1) track information on genomic applications in health practice; 2) facilitate the uptake and use of objective information from evidence reviews and technology assessments in a variety of healthcare settings; 3) identify additional knowledge gaps that drive clinical and population research; 4) highlight the need for targeted research on the clinical validity and utility of these candidate applications; 5) provide emerging knowledge to support best practices through policy development and education; and 6) highlight the need

for post-market population surveillance and applied research. GAPPNet would not replace, but complement and partner with, the many coordinating efforts in genomics already ongoing in the U.S. among both professional specialty organizations (e.g. American College of Medical Genetics), advisory groups to the government (e.g. Secretary's Advisory Committee on genetics, health and Society, SACHGS) and multi-group entities (partial list in table 3). GAPPNet will provide a stakeholder forum for these groups towards the goal of genomic integration into health care and disease prevention. In addition, GAPPNet will interface with international collaborations (e.g., with the Genome-based Research and Population Health International Network (GRAPHInt, 14), and international health technology assessment groups (15).

It is important to acknowledge at the outset that genomics technologies need to be put in the larger context of current healthcare delivery issues. Genomic technologies are no different from other healthcare technologies and they need to follow principles of evidence based medicine and comparative effectiveness. Therefore, GAPPNet could also leverage several ongoing non-genomic healthcare federal and nonfederal initiatives to integrate gene-based applications in the context of medicine and population health (e.g. 16-22).

### **GAPPNet Activities**

Details of how GAPPNet will be set up and operated will be discussed over the next few months by the GAPPNet planning group. In brief, GAPPNet will develop a process that links ongoing collection of information on candidate genomic applications to 4 crucial

domains: 1) knowledge synthesis and dissemination for new and existing technologies, and the identification of knowledge gaps, 2) a robust evidence-based recommendation development process (EGAPP initiative-see below), 3) translation research to evaluate validity, utility and impact in the real world and how to disseminate and implement recommended genomic applications (23) , and 4) programs to enhance practice, education and surveillance. Key to the success of GAPPNet is an expanded stakeholder group to ensure collaboration and representation of multiple viewpoints. The interrelationship of GAPPNet domains is shown in Figure 1.

### ***GAPPNet Domain 1: Knowledge Synthesis and Dissemination***

GAPPNet will promote the objective synthesis and timely dissemination of information on candidate health applications of genome-based tests and technologies. A central website (the GAPPNet knowledge base) will maintain and update a list of these applications with links to partner websites and available credible information (e.g. GeneTests (24)). GAPPNet will expand the information base on genomic application topics that have been identified and/or reviewed by the EGAPP working group (see below). GAPPNet will sponsor a knowledge synthesis process that uses and adapts methods of horizon scan and rapid systematic reviews developed by EGAPP. This process will use standardized formats to synthesize and update available information on these applications. For each suggested application and health-related scenario, information will be accumulated on analytic validity, clinical validity, clinical and public health utility using methodologies of systematic reviews and evaluations. When evidence based reviews have been conducted by EGAPP or other

Health Technology Assessment groups such as the US Preventive Services Task Force (25) the website will provide links to these reviews. In the absence of comprehensive reviews, brief reports of selected promising genomic applications, e.g., those identified by EGAPP horizon scans will be provided. When no information is available, this will also be pointed out. The GAPPNet knowledge base thus will provide an initial and credible stop for users to scan for information on available genomic applications and what we know and what we don't know with respect to their analytic and clinical performance. GAPPNet collaborators conducting research and evaluation (see below) will provide important contributions to the GAPPNet knowledge base contents and dissemination. Partnerships will be sought with key medical and public health journals to publish results of knowledge synthesis evaluations similar to the current arrangement the EGAPP Working Group has with this Journal, a pioneer in the intersection of genomic medicine and evidence-based medicine. A GAPPNet knowledge base working group will be formed to determine the content and curate the site.

A related and crucial function is the systematic and active dissemination of the knowledge base to consumers, policy makers and providers. Statements relating the evidence supporting an application (or lack thereof) will be made available on an ongoing basis to inform provider and consumer choices. Further, it is anticipated that these statements will be used to support the development of clinical decision support (CDS) tools for clinical practice and disease prevention. To this end, GAPPNet will actively engage professional organizations related to the fields of practice (e.g., family practice, oncology, cardiology, etc), as well as relevant stakeholders from health informatics. The EGAPP Stakeholder

Group, made up of over 30 professionals, has already made an impressive start on this work (see below).

### ***GAPPNet Domain 2: Evidence-based recommendation development***

EGAPP represents a fundamental building block for GAPPNet. In 2004, CDC launched the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) initiative (26). The main goal of EGAPP is to establish and test a systematic, evidence-based process for evaluating genetic tests and other applications of genomic technologies that are in transition from research to clinical and public health practice. EGAPP has integrated existing recommendations on the evaluation of interventions from professional organizations and advisory committees, task forces (e.g., US Preventive Services Task Force, CDC's Task Force on Community Preventive Services), and international health technology assessment groups. EGAPP activities are focused around the independent, non-federal EGAPP Working Group established in 2005. The roles of this multidisciplinary panel include developing methods and processes for evidence reviews of complex and rapidly emerging technologies, including, identification, prioritization and selection of topics, guidance of the conduct of evidence reviews, and development of recommendations for clinical and public health practitioners based on the evidence (27). In 2007, four evidence reports were completed: i) genomic tests for detection and management of ovarian cancer; ii) testing for CYP450 polymorphisms in adults with non-psychotic depression treated with SSRIs; iii) hereditary nonpolyposis colorectal cancer: diagnostic strategies and their implications; and iv) impact of gene expression profiling tests on breast cancer outcomes. Another report on *UGT1A1*

genotyping and morbidity and mortality in patients with metastatic colorectal cancer treated with irinotecan, and a supplemental report, DNA testing strategies aimed at reducing morbidity and mortality from Lynch Syndrome, are in press. Based on consideration of the information provided by the evidence report and significant clinical and social contextual issues about a specific genetic test, the EGAPP Working Group develops a recommendation statement that summarizes the current knowledge about the validity and utility of the genetic test, provides guidance on appropriate use of the test, and defines key knowledge gaps and needed research. In 2007, the first in a series of EGAPP Working Group recommendation statements was published on CYP450 testing in patients with depression treated with SSRIs. Other reports are forthcoming in this journal.

An EGAPP Stakeholders Group was set up in 2005 to provide feedback to the Working Group, assists with dissemination of the recommendation statements to various organizations. The Stakeholders Group includes representatives from academia, health care and public health professionals, health care payers and plans, policy makers, media, consumer advocacy groups, business, the biotechnology industry, educators, and information technology developers. The broad-based EGAPP Stakeholder Group will be a key component of GAPPNet in supporting the dissemination of evidence-based recommendations and the implementation of those recommendations into practice with their constituent stakeholder groups. In addition, the Stakeholder Group will be able to support dissemination of credible information on genomic applications for which evidence is lacking about their validity and/or utility. We envision that the GAPPNet stakeholder group will be build on the

current EGAPP stakeholder group to include representatives from other initiatives (e.g. Table 3)

### ***GAPPNet Domain 3: Translation Research***

An important feature of GAPPNet is the promotion of translation research in multiple disciplines needed to close the knowledge gaps about candidate genomic applications in practice. For example, Table 3 shows a partial list of questions which must be addressed by researchers in multiple scientific disciplines in order to assess the utility of genome-wide profiles for risk assessment and disease prevention and how to disseminate and implement recommended genomic applications. Basic and translation research could be sponsored by federal agencies, the private sector or public-private partnerships. A substantial start on early translation research regarding issues in genetic epidemiology surrounding GWAS has been made by the Office of Population Genomics (OPG) of the National Human Genome Research Institute (<http://www.genome.gov/19518660>). Addition of GWA genotyping to existing case-control studies, cohort studies, clinical trials, and biorepositories, and cataloguing of results of GWAS (<http://www.genome.gov/26525384>), will help to develop and synthesize genomic knowledge for clinical applications. Despite these efforts, The EGAPP initiative has uncovered major gaps in our knowledge base on the clinical validity and utility of even the most promising genomic applications in practice and prevention. Between 2001 and 2006, the USPSTF recommended only one genetic test for use in primary care, largely due to a lack of a sufficient evidence base (28). Implementation of existing and new guidelines is also problematic. This is not unique to genomic applications; only half of

all adults in the U.S. receive recommended clinical preventive services, and just over half receive recommended care for acute and chronic conditions (e.g., 29-31). Therefore, research and evaluation of the dissemination and implementation of evidence recommendations relevant to genomic applications is essential. Absent such research, potential health benefits are unlikely to be fully realized throughout the U.S. population.

We envision that recipients of current and planned translation research will become the initial nucleus of GAPPNet investigators, not only for conducting primary research in genomics translation, but also for contributing expert knowledge synthesis and dissemination of research findings for use in health practice. A core group of such investigators already exists – and is growing. Recognizing the existing evidence and dissemination dilemma in genomic medicine, the CDC recently launched a translation research initiative in genomics to fund multiple groups to conduct translation research projects (32). This initiative focuses on the content identified through the genomic application horizon scans developed by the EGAPP Working Group and other tests and applications examined by USPSTF. These applications include the use of family history as a tool for disease prevention. Starting in 2009, several groups will be funded to conduct crucial research on candidate health applications. Some investigators might be groups already funded through NHGRI's Population genomics and ELSI programs. In addition, several NIH initiatives have recently been announced. For example, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the NIH recently announced the availability of grants under the Secretary of Health and Human Services' 'Genes, Environment, and Health Initiative' (GEI), to conduct translation research to use results of new gene discoveries in clinical practice,

psychosocial research as well as education and communication research (33). Also, the National Cancer Institute at NIH currently is funding a number of investigators conducting translation research in genomics and personalized medicine, and has several program announcements in this area (e.g., 34, 35). The National Heart, Lung and Blood Institute (NHLBI) is conducting translation research on warfarin. In 2007, the FDA changed the labeling of warfarin to indicate that genetic information may affect warfarin dosing. Genetic information combined with clinical information may enhance patient treatment and outcomes, and personalize warfarin treatment for each individual. In a proof-of-concept study, NHLBI recently awarded a contract to conduct a large, multicenter, double-blind randomized trial of genotype-guided dosing of warfarin therapy which is currently under way (36). Investigators from each of these new initiatives are excellent candidates for participation in GAPPNet.

#### ***GAPPNet Domain 4: Programs to Enhance Practice, Education and Surveillance***

In addition to building and disseminating a knowledge base and empowering translation research, GAPPNet will empower and promote translation programs focused on the implementation of validated genomic applications in practice and prevention. Health information technology has been identified as a key aspect of the genomics translation process, and there are a number of ongoing national activities designed to leverage health information technology to support genomics translation efforts (3). These activities will be conducted in population and clinical practice settings in the U.S. In 2008, CDC released an RFA to sponsor multiple groups including academia, health departments, as well as practice settings to perform such activities (37). Funding will be awarded in 2009. In addition,

several groups are already conducting educational efforts and surveillance (some mentioned in Table 1). For example, the National Human Genome Research Institute of the NIH has awarded a contract for the development of a web-based curricular tool for interdisciplinary genomics education for nurses and physician assistant educators. Also, the Agency for Healthcare Research Quality (AHRQ) recently announced a new award to develop, implement and evaluate four computer-based decision-support tools that will help clinicians and patients better use genetic tests to evaluate and treat breast cancer. The first tool will assess whether a woman with a family history of cancer should be tested for *BRCA1* and *BRCA2* gene mutations. The second tool will be used for women already diagnosed with breast cancer, will help determine which patients are appropriate for gene expression profiling test (38).

GAPPNet will interact with these groups to promote work related to the emerging list of candidate genomic applications in the knowledge database, especially the ones for which evidence based guidelines have been developed. For example, with respect to the use of *BRCA1* testing in women at high risk because of family history, we currently have little evidence to date on utilization and impact on health outcomes in practice. Such programs are crucial in documenting attitudes, awareness and knowledge of consumers and providers, tracking integration and impact of genomic applications in practice as well as documenting and addressing issues of health disparities. The EGAPP Stakeholder Group and the initial cohort of CDC- and NIH-funded investigators will become active collaborators in GAPPNet and a cornerstone for its further development.

Examples of genomics translation programs activities are shown in Table 2. One illustration is the public health surveillance of consumer and provider awareness and use of DTC tests. For the past few years, the CDC and several health departments have conducted a number of state and national surveys to assess knowledge, attitudes, and practices of such tests (e.g., BRCA1 (39) and nutrigenomic tests (40)). Conducting translation research and programs will contribute valuable information to the knowledge base of “what works and what does not work” on the impact of genomic applications on health outcomes in the real world. Such an experience will stimulate additional research to close the knowledge gaps in genomic applications in practice and prevention.

### **Concluding remarks**

In spite of the rapid evolution and success of human genome discoveries, the pace of implementation of genome-based applications in healthcare and population health has been slow. Major gaps exist in our understanding of how new knowledge of human genetic variation can be most effectively harnessed to improve health and prevent disease. We believe that GAPPNet will help to catalyze productive interactions between existing and emerging translational research efforts, thereby speeding knowledge base expansion and driving the dissemination of information for disease treatment and prevention. To further develop GAPPNet, CDC and NIH will sponsor a number of stakeholder meetings to discuss goals, synergize activities, and develop specific action plans. In the meantime, readers of this article interested in the mission and vision of GAPPNet can find more information on the CDC public health genomics website at <http://www.cdc.gov/genomics>.

## References

1. Manolio TA, Brook LD, Collins FS. A HapMap harvest of insights into the genetics of common disease. *J Clin Invest*. 2008;118:1590-605.
2. Feero WG, Guttmacher AE, Collins FS. The genome gets personal-almost. *JAMA* 2008;299:1351-1352.
3. Department of Health and Human Services: personalized healthcare initiative. Accessed online July 21, 2008 at: <http://www.hhs.gov/myhealthcare/>
4. Secretary's Advisory Committee on Genetics, Health and Society. US system of oversight of genetic testing. Accessed online July 21, 2008 at: [http://www4.od.nih.gov/oba/SACGHS/reports/SACGHS\\_oversight\\_report.pdf](http://www4.od.nih.gov/oba/SACGHS/reports/SACGHS_oversight_report.pdf)
5. Khoury MJ, Bradley L, Berg A, et al. The evidence dilemma in genomic medicine: the need for a roadmap for translating genomic discoveries into clinical practice. *Health Affairs* 2008 (in press).
6. Hudson KL, Holohan MK, Collins FS. Keeping pace with the times--the Genetic Information Nondiscrimination Act of 2008. *N Engl J Med*. 2008;358:2661-3.
7. Hogarth S, Javitt, Melzer D. The Current Landscape for Direct-to-Consumer Genetic Testing: Legal, Ethical, and Policy Issues. *Ann Rev Genom Hum Genet* 2008; 9: 161-182.
8. McGuire AL, Cho MK, McGuire SE et al. The future of personal genomics. *Science* 2007;317:1687.
9. Hunter DJ, Khoury MJ, Drazen JM. Letting the genome out of the bottle--will we get our wish, *New Engl J Med* 2008;358:105-107.

10. Agency for Healthcare Research and Quality. United States Preventive Services Task Force: Screening for hemochromatosis, 2006. Accessed online October 10, 2008 at <http://www.ahrq.gov/clinic/uspstf/uspshemoch.htm>.
11. Agency for Healthcare Research and Quality. Infrastructure to monitor utilization and outcomes of gene-based applications: an assessment. 2008. Accessed online October 10 at: <http://effectivehealthcare.ahrq.gov/healthInfo.cfm?infotype=nr&ProcessID=63>
12. Westfall JM, Mold J, Fagman L. Practice-based research-“blue highways” on the NIH road map. JAMA 2007;297:403-406.
13. Sung NS, Crowley WF, Genel M, et al. central challenges facing the national clinical research enterprise. JAMA 2003;289:1278-1287.
14. Genome-based research and population health International Network (GRaPHInt). Accessed online July 21, 2008 at: <http://www.graphint.org>
15. Health Technology Assessment International. Accessed online August 5, 2008 at: <http://www.htai.org/>
16. Agency for Healthcare Research and Quality. Effective healthcare program. Accessed online at (<http://effectivehealthcare.ahrq.gov/aboutUs.cfm?abouttype=program>
17. Centers for Medicare and Medicaid Services. Coverage with evidence development. Accessed online October 10, 2008 at: [http://www.cms.hhs.gov/CoverageGenInfo/03\\_CED.asp](http://www.cms.hhs.gov/CoverageGenInfo/03_CED.asp)
18. Food and Drug Administration. Sentinel Initiative. Accessed online October 10, 2008 at: <http://www.fda.gov/oc/initiatives/advance/sentinel/>
19. Health Resources and Services Administration. Maternal and Child Health Bureau. <http://mchb.hrsa.gov/programs/>

20. National Institutes of Health. Clinical and Translational Sciences Awards. Accessed online October 10, 2008 at:  
[http://www.ncrr.nih.gov/clinical\\_research\\_resources/clinical\\_and\\_translational\\_sciences\\_awards/](http://www.ncrr.nih.gov/clinical_research_resources/clinical_and_translational_sciences_awards/)
21. Institute of Medicine Roundtable on Evidence-based Medicine. Accessed online October 10, 2008 at: <http://www.iom.edu/CMS/28312/RT-EBM.aspx>
22. Foundation for the National Institute of Health. Observational Medical Outcomes Partnership. Accessed online October 10, 2008 at:  
[http://www.fnih.org/index.php?option=com\\_content&task=view&id=508&Itemid=643](http://www.fnih.org/index.php?option=com_content&task=view&id=508&Itemid=643).
23. Khoury MJ, Gwinn M, Yoon PW, Dowling N, Moore, CA, Bradley C: The continuum of translation research in genomic medicine” how can we accelerate the appropriate integration of human genome discoveries into health care and disease prevention? *Genet Med* 2007;9: 665-674.
24. GeneTests. Accessed online August 5, 2008 at:
25. Agency for Healthcare Quality Research. US Task Force on Preventive Services. Accessed 8/5/08 at: <http://www.ahrq.gov/clinic/USpstfix.htm>
26. Evaluation of Genomic Applications in Practice and Prevention (EGAPP). Accessed online August 5, 2008 at: <http://www.egappreviews.org/>
27. Teutsch SM, Bradley LA, Palomaki G, et al. The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) initiative: methods of the EGAPP working group. *Genet Med* 2008;epub, online access at:  
<http://www.geneticsinmedicine.org/pt/re/gim/pdfhandler.00125817-9000000000->

[99948.pdf;jsessionid=JDyQWLv0TjJ1GhQ6VdrPmhDs19KpDI7spJhLnXpsZJ8jf2TFwJrJ!-1891305337!181195628!8091!-1](#)

28. Nelson HD, Huffman LH, Fu R, et al. Genetic risk assessment and BRCA mutation testing for breast and ovarian cancer susceptibility: systematic evidence review for the U.S. Preventive Services Task Force. *Ann Int Med* 2005;143:362-379.
29. Reid PP, Compton WD, Grossman JH, Fanjiang G (eds). Building a better delivery system. National Academy of Sciences. National Academies Press, Washington, DC, 2005.
30. Schuster MA, McGlynn EA, Brook RH. How good is the quality of health care in the United States. *Milbank Quarterly* 2005;83(4):843-95).
31. McGlynn EA, Asch SM, Adams J, et al. The quality of health care delivered to adults in the United States. *NEJM* 2003;348:2635-45)
32. Centers for Disease Control and Prevention. Genomic Applications in Practice and Prevention Translation Research. Funding announcement. Accessed online August 5, 2008 at: [http://www.cdc.gov/genomics/activities/fund2007\\_11\\_29.htm](http://www.cdc.gov/genomics/activities/fund2007_11_29.htm)
33. National Institutes of Health. Funding announcement. Translation of Common Disease Genetics into Clinical Applications. Accessed online August 5, 2008 at: <http://grants.nih.gov/grants/guide/rfa-files/RFA-DK-08-004.html>
34. National Cancer Institute. Program Announcements on Development, Application, and Evaluation of Prediction Models for Cancer Risk and Prognosis <http://grants.nih.gov/grants/guide/pa-files/PA-07-021.html>
35. National Cancer Institute. Program Announcement: Understanding the Effects of Emerging Cellular, Molecular, and Genomic Technologies on Cancer Health Care

- Delivery. Accessed August 5, 2008 at: <http://grants.nih.gov/grants/guide/pa-files/PA-07-260.html>
36. University of Pennsylvania. National Heart, Lung and Blood Institute. Genotyped guided dosing of warfarin clinical trial. Accessed online September 22, 2008 at: <http://rt5.cceb.med.upenn.edu/warfdcc/WARF-1.html>
37. Centers for Disease Control and Prevention. Genomic Applications in Practice and Prevention Translation programs in education, surveillance, policy. Funding announcement. Accessed online August 5, 2008 at: <http://www.cdc.gov/od/pgo/funding/GD08-801.htm>
38. Agency for Healthcare Research Quality. Computer-based Clinical Decision Support (CDS) Tools for Gene-based Tests Used in Breast Cancer. Accessed online September 29, 2008 at: <http://effectivehealthcare.ahrq.gov/healthInfo.cfm?infotype=nr&ProcessID=68>
39. Myers M, Chang MH, Jorgensen C, et al. Genetic testing for susceptibility to breast and ovarian cancer: evaluating the impact of direct to consumer marketing campaign on physicians' knowledge and practices. *Genet Med* 2006;8:361-370.
40. Goddard KAB, Moore C, Ottman D, et al. Awareness and use of direct to consumer nutrigenomic tests: United States 2006. *Genet Med* 2007;9:510-517.
41. Institute of Medicine. Roundtable on translating genome-based research for health. Accessed online August 5, 2008 at: <http://www.iom.edu/CMS/3740/44443.aspx>
42. American Public Health Association. Genomics Forum. Accessed online August 5, 2008 at: <http://aphagenomicsforum.org/index.php?note=AboutUs>

43. National Coalition for Health Professional Education in Genetics. Accessed online August 5, 2008 at: <http://www.nchpeg.org/>
44. Genetic Alliance. Accessed online August 5, 2008 at:  
<http://www.geneticalliance.org/>
45. Personalized Medicine Coalition. Accessed online August 5, 2008 at:  
<http://www.personalizedmedicinecoalition.org/>
46. Centers for Disease Control and Prevention. National Office of Public Health Genomics. Genomics in Practice. Accessed online August 5, 2008 at:  
<http://www.cdc.gov/genomics/phpractice.htm>

Table 1

**Examples of Multidisciplinary Translation Research Needed for Evaluating Genome-Wide Profiles for Risk Assessment and Disease Prevention**

<b>Field</b>	<b>Scientific Research</b>	<b>Current Issues</b>
<b>Epidemiology</b>	<b>Genotype prevalence, calculating risks associated with genetic variants, gene-gene and gene environment interactions</b>	<b>Data currently lacking on magnitudes of risks especially for joint effects of genes and environment</b>
<b>Clinical Evaluation</b>	<b>Quantify added value of genome wide profiles, in predicting risks especially compared with traditional risk factors (sensitivity, specificity, predictive values)</b>	<b>Data currently suggest weak discriminatory ability of genome profiles compared with traditional risk factors and intermediate disease markers. Also it is not clear what is the net benefits versus harms in using genome profiles</b>
<b>Behavioral &amp; Social Sciences</b>	<b>Assess how genome profiles affect behavior of individuals, families and populations</b>	<b>Data from other fields suggest that behavior change is difficult. It is not clear if genome information matters</b>
<b>Communication Sciences</b>	<b>Study communication and education strategies for using genomic information to improve health</b>	<b>Provider and consumers are not equipped to deal with this type of information</b>
<b>Outcomes Research &amp; Public Health Surveillance</b>	<b>Assess impact of genome info health outcomes in the real world, health disparities, and economic indicators</b>	<b>Expensive technology when applied on population basis; unknown health benefits and potential harms</b>

**Table 2**  
**The Genomic Applications in Practice and Prevention Network (GAPPNet)**

Question	Description and examples
What is it?	Collaboration of individuals and organizations interested in translating appropriately-validated genomic applications into practice and prevention in the United States.
What is the vision?	To realize the promise of genomics in treating and preventing disease, improving health, and reducing health disparities
What is the mission?	To accelerate and streamline the effective integration of validated genomic knowledge into the practice of medicine and public health in the United States, by empowering research and evaluation, and disseminating high quality information on promising genomic applications in practice and prevention.
Who are the members?	Initial group of genomics translation grant awardees from NIH, CDC and other groups; various stakeholders groups; GAPPNet knowledge synthesis developers; other collaborators
Who are the conveners?	CDC and NIH
What are the domains of GAPPNet?	
1. Knowledge Synthesis & Dissemination	Integration of evidence reviews and recommendations into clinical decision support tools via the development of GAPPNet knowledge database
2. Evidence-based guideline development	Evaluation of Genomic Applications in Practice and Prevention (EGAPP) working group provides independent assessment, develops guidelines and identifies knowledge gap
3. Translation research	Evaluating clinical utility of pharmacogenomics (e.g. <i>VKOR</i> and <i>CYP2C9</i> testing as an adjunct to anticoagulation). Evaluating the effectiveness of interventions to increase the implementation of evidence-based tests (e.g. <i>BRCA1</i> )
4. Translation programs	Promote development and implementation of model programs (e.g. integrating validated genomic applications in primary care). Sponsoring educational activities for providers (e.g. appropriate use of <i>BRCA1</i> testing). Promote the conduct of population health surveillance (e.g. direct to consumer impact of personal genomics)

**Table 3****Ongoing selected multi-group efforts in translating genomic discoveries into population health and health care in the United States**

Effort (ref)	Mission/Purpose	Members	Activities
IOM Genomics Roundtable (41)	“To advance the field of genomics and improve the translation of research findings to health care, education, and policy”	Multiple	Workshops
APHA Genomics Forum (42)	Members of the American Public Health Association interested in raising awareness and competencies of genetics in public health	Public health	Committees Policy Statements
NCHPEG (43)	“To promote health professional education and access to information about advances in human genetics to improve the health care of the nation”	Multiple	Annual meetings, educational projects
Genetic Alliance (44)	Coalition of genetics support groups to “build capacity in advocacy, and to educate policy makers”	Disease support groups	Annual meeting policy statements special projects
Personalized Medicine Coalition (45)	“To advance understanding and adoption of personalized medicine for the ultimate benefit of patients”	Multiple	Meetings, reports, advocacy
Network of State Health Departments and Schools of Public Health (46)	CDC funded projects to integrate genomics into public health programs with a focus on chronic diseases	4 states 2 Schools	Training surveillance education

**Figure 1**  
**The Genomic Applications in Practice and Prevention Network (GAPPNet)**

