The path from genome-based research to population health: Development of an international public health genomics network

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The health benefits of the Human Genome Project have been widely anticipated. Experts predict a new era of individualized disease prevention based on testing for genetic susceptibilities,¹ and safer, more effective use of drugs based on pharmacogenomic testing.² Genomic research is also predicted to improve disease classification and generate innovative therapies, targeted more precisely to the molecular mechanisms of disease.³

Early breakthroughs support this promise. Genetic testing can identify women at high risk for breast and ovarian cancer who may benefit from interventions such as breast screening by MRI and prophylactic oophorectomy.⁴ Pharmacogenomic testing offers a potential means to increase the safety of drugs with narrow therapeutic indices, such as mercapotopurines⁵ and warfarin.^{6,7} Genetic analysis of disease processes such as cancer has also provided benefit: Overexpression of the *HER2/ neu* gene provides an important prognostic indicator in breast cancer, and identifies patients most likely to benefit from the groundbreaking drug herceptin.⁸ Similarly, imatinib mesylate, a novel cancer therapy, was developed as a result of analysis of the genetic changes in a specific type of leukemia.⁹

Despite these impressive early advances, serious reservations have been voiced about the occurrence and timing of a genomics revolution in medicine.¹⁰ The relationship between DNA sequence and phenotype is far from simple, even for highly penetrant single gene conditions.^{11,12} Most individual gene variants associated with common diseases will have low positive predictive value and associated attributable risk, raising questions about their clinical utility.^{10,13,14} Also, an overemphasis on genetic contributors to disease may result in neglect of other factors, such as environmental exposures, social structure and lifestyle.¹⁰

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Which vision of the future should the prudent clinician believe: A cornucopia of healthcare innovations based on genomic research, or a stream of genetically-based interventions that fail to deliver value to the public? We argue that both visions are correct; that genome-based research will offer unprecedented opportunities for improved disease prevention and therapy, but will also generate many promising ideas that do not ultimately provide a health benefit.

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As with other emerging technologies, the pressing challenge is to devise an efficient strategy to distinguish innovative advances from false leads. The stakes are high, as healthcare systems face increasing strains with growing elderly populations and chronic disease burdens.¹⁵ The potential benefits offered by the Human Genome Project and advances in related technologies need to be weighed against the resources required to implement them and the potential harms.

In this paper, we review the challenges in using genomebased research for the benefit of population health, make the case for an interdisciplinary knowledge integration process under the rubric of a field variously dubbed "public health genetics" or "public health genomics," which is poised to address these challenges, and discuss the development of an international initiative to promote a collaborative approach to harness genome-based knowledge for the benefit of worldwide population health.

USING GENOME-BASED RESEARCH TO IMPROVE HEALTH

Limitations in genetic prediction

Diseases due to single gene mutations are generally rare; for example, *BRCA1* and *BRCA2* mutations account for only 3–10% of breast cancer cases overall.¹⁶ A somewhat larger proportion of diseases can be considered oligogenic, with disease risk due to the effects of a relatively small number of gene variants. For most diseases, however, etiology is multifactorial, with numerous genetic influences interacting with many different social and environmental factors. The specific gene variants contributing to disease, and the relative importance of genetic and nongenetic factors, may vary considerably among different people with a given disease. Because of the complexity of multifactorial disease etiology, there are inherent limitations in the potential for genetics to predict health status.

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The key role of interventions

In addition, even when a genetic risk is substantial, knowledge of the risk contributes to improved health outcomes only if effective measures are available for preventive or early treatment. For example, APOE genotyping can identify an increased risk for Alzheimer Disease (AD),17 but does not provide a health benefit because no preventive interventions are known. Moreover, despite the increased risk, a positive result is of relatively low predictive value; many people without the APOE4 allele associated with AD risk will also develop the disease. However, some people are likely to seek this risk information,¹⁸ and it may provide some benefit by allowing people to make personal and family decisions based on risk knowledge. From a public health perspective, use of genetic tests for this purpose requires rigorous and systematic evaluation, to determine whether the benefits justify the potential harms and opportunity costs.

Similarly, genetic testing is of uncertain value when the available interventions are not genotype-specific. For example, people with factor V Leiden or the prothrombin variant G20210A have an increased risk for venous thrombosis (VT).¹⁹ However, current data suggest that their recurrence risk for VT is not significantly elevated compared to other patients with VT.²⁰ As a result, genetic testing is not needed for clinical management.

Genetic testing will have its greatest public health value when it identifies individuals who would benefit from specific interventions based on their risk. This paradigm is the basis for newborn screening, and for the use of a small number of genetic tests, such as *BRCA* testing, which have become a part of clinical practice. By this reasoning, the public health value of *APOE* genotyping would increase if a specific therapy were identified to reduce AD risk in people with the *APOE4* allele.

Could genetic risk be a motivator for behavioral change?

Even without genotype-specific interventions, some experts propose that knowledge of genetic risk can inform individuals about the lifestyle changes most beneficial for them, letting them know what health risks to worry about. This intuitively appealing argument is a hypothesis that remains to be tested.²¹ The limited available data offer mixed results. Genetic tests identifying an increased risk for lung cancer do not appear to result in increased smoking cessation.^{22,23} Conversely, genetic risk information may motivate participation in preventive screening: several studies have shown that the likelihood of participating in colorectal cancer screening is positively associated with having a family history of the disease.^{24–28}

False reassurance is a risk of this approach. When genetic risk is emphasized, a test showing the absence of genetic risk for a condition such as cardiovascular disease, diabetes or cancer could send the message that there is no need to worry about that particular risk, yet the negative predictive value of such tests is likely to be very low.

Clearly, further research is needed. With the right combination of risk information and behavioral interventions, progress in lifestyle change might be possible. An important question from the population perspective will be the feasibility of using genetics to subcategorize populations, in order to achieve greater efficiency by directing appropriate interventions to those subpopulations rather than to the whole population.

Other uses of genetic information to improve health outcome

In addition to information about individual susceptibilities, genome-based research is generating knowledge about somatic genetic changes including somatic mutations occurring during carcinogenesis and profiles of gene expression that characterize specific disease states. This research may provide the basis for innovative drug development and for diagnostic and prognostic tests that guide clinical management. As with genetic susceptibility testing, careful evaluation of the predictive value of such tests and the effectiveness of related therapeutics or other interventions will be needed.

Genetic exceptionalism and the isolation of ELSI research

One of the challenges in the evaluation of genomic applications to healthcare is the integration of studies of the ethical, legal and social implications (ELSI) with those of clinical outcomes. The Human Genome Project allocated funds toward ELSI research and a vast amount of literature has resulted, but the separation of ELSI research from other scientific and clinical spheres has hampered a constructive contribution of ELSI research to the goal of improving population health. An example is the ACCE framework proposed for evaluation of genetic tests,²⁹ in which the scientific and clinical evaluation are considered separately from the ethical, legal and social consequences of a test, without guidance as to how these different spheres should inform each other.

This separation may be an outcome of "genetic exceptionalism,"³⁰ the concept that genetic information is uniquely powerful, and also uniquely dangerous and frightening, resulting in the need for special protections. This concept appears to result from the considerable hype, both positive and negative, that has surrounded the human genome project. Exaggerated claims about the predictive power of genetic information have been met by equally exaggerated warnings about the consequences of its misuse.

NEED FOR AN EVALUATION STRATEGY

As genome-based research generates new ideas for healthcare innovation, there is a critical need for an evaluation process, based in ongoing integration of knowledge within and across multiple disciplines (including ELSI) to determine the outcomes, both health-related and social, of new genomebased applications. In the absence of a robust evaluation strategy, a trial-and-error process of innovation occurs. Resulting commercial incentives tend to promote the value of genetic tests based on the intuitive appeal of risk knowledge in the absence of proven benefit. This approach is already evident in direct-to-consumer and -physician marketing of genetic tests,^{31,32} and represents a potential drain on healthcare resources. There is also a risk that effective innovations will not be implemented, or implemented haphazardly.^{33,34}

THE PUBLIC HEALTH GENOMICS ENTERPRISE

With these challenges in mind, an international expert workshop was convened in April, 2005, in Bellagio, Italy. The workshop was attended by a multidisciplinary group of 18 experts from Canada, France, Germany, the United Kingdom and the United States. A full report of the discussions and conclusions of the Bellagio workshop is available.³⁵ Participants at the meeting developed a consensus on the structure needed for effective translation of genome-based science and technology into improved population health. Figure 1 shows this concept in visual form.

The central role of knowledge integration

Knowledge integration, both within and across disciplines, is the driving force of the public health genomics enterprise. It is defined as the process of selecting, storing, collating, analyzing, integrating and disseminating information both within and across disciplines for the benefit of population health. It includes methodological development, and is the means by which information is transformed into useful knowledge.

Integration of knowledge within a discipline: HuGENet as a model

Genetic epidemiology offers an example of knowledge integration. This field has been dominated over the past 10–15 years by the search for associations between specific genetic variants and disease. The experience to date indicates that many initial reports of gene-disease associations are false-positive findings. Thus, before clinical applications can be considered, all the accumulated knowledge about a set of gene variants must be carefully assessed, including prevalence in different populations, the strength of the association with different disease endpoints, and interactions between gene variants and social and environmental determinants of risk. HuGENet (Human Genome Epidemiology

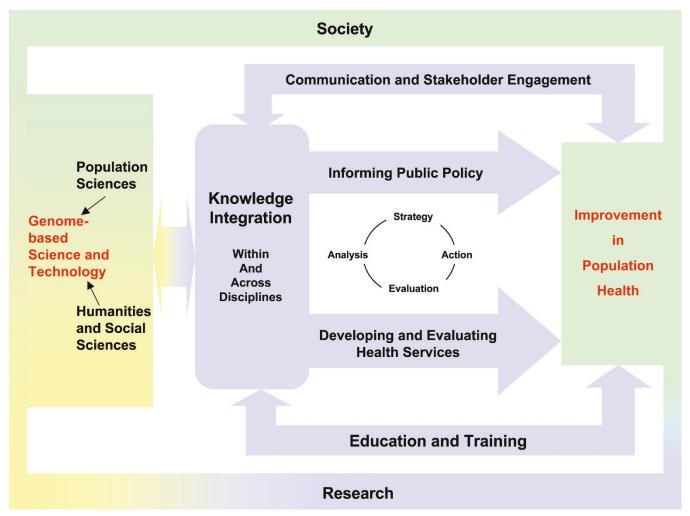


Fig. 1. Components of the public health genomics enterprise. The functions and activities shown in blue represent the scope of the enterprise of public health genomics, which can be simply defined as the effective and responsible translation of genome-based knowledge and technologies for the benefit of population health. Initiatives in several countries have already begun this effort (Appendix 1.1). The color yellow represents the generation of knowledge through research; genome-based science and technology (highlighted in red) play a fundamental role. Any new development in modern genomics, or in molecular or cell biology, can legitimately be considered as a potential contributor to innovative approaches to achieving population health. Green represents all the activities, people, institutions and views that make up society in its widest sense, comprising key stakeholders in the success of the translational process.

July 2006 · Vol. 8 · No. 7

Burke et al.

Network), an initiative of the Office for Genomics and Disease Prevention (ODGP) at the US Centers for Disease Control and Prevention in Atlanta, GA, provides the basis for a constructive approach to this problem, and also represents a model for international collaborative efforts in other research areas.

HuGENet is now an international network comprising nearly 800 collaborators in 43 countries, with core activities consisting of information exchange through its website,36 training and technical assistance, knowledge base development and information dissemination. As of December, 2005, 42 HuGE reviews have been published, each providing a structured and systematic summary of human genetic variation and its health implications at one or more gene loci.36 In addition, more than 286 systematic reviews - including meta-analysis or pooled analyses - of gene-disease associations have been published since 2001.36 An important function of these reviews is to identify gaps in existing epidemiological and clinical knowledge, informing the future research agenda. The structure of HuGENet is currently being revised along the lines of the highly successful international Cochrane Collaboration. Several HuGENet coordinating centers are being developed including Cambridge, Ottawa and Ioanina. Projects are underway to develop new systems for capturing and storing relevant data in an appropriate format for use in meta-analyses and systematic reviews.37,38

A related initiative, the Public Population Project in Genomics (P3G), has recently been launched.³⁹ This project has the goal of providing the international population genomics community with the resources, tools and know-how to facilitate data management for improved methods of knowledge transfer and sharing. Regular members are international, national or regional not-for-profit organizations that are or will be conducting a large population (N > 10,000 samples) genomics projects. Not-for-profit organizations and individuals committed to population genomics research genomics can join as Associate or Individual members.

Other disciplines might benefit from taking this coordinated approach. Genetic test evaluation is being approached piecemeal throughout the world, with initiatives using varying methodologies now underway under the auspices of both the European Union and the Organization for Economic Cooperation and Development, as well as in many individual countries including Canada, the UK and the US. Coordinating these activities through international networks like HuGENet and P3G would allow sharing of expertise and avoid wasteful duplication. Similarly, a joint approach to sustainable integration of genetics into existing mainstream medical specialties may be helpful.^{40–42}

Integration of knowledge across disciplines

Creating productive collaboration in a single discipline is only the first step in knowledge integration. Knowledge and insight from many disciplines will be needed to fully evaluate the potential for genome-based research to improve population health. (Fig. 1). Both medical and social outcomes of test use must be considered, and appropriate procedures must be implemented for practice guideline development, decisionmaking by healthcare payers, and population-based consultation and education. In addition, current ethical and regulatory frameworks need to be assessed for their appropriateness to new conceptual and technologic approaches based on genomic research.

Achieving knowledge integration across disciplines is not easy, but is essential to the tasks of public health genomics. Each discipline has its own language and means of communication, its own standards for success, and its own methods for sharing and discussing ideas and concepts. In addressing this problem, the Bellagio workshop participants found it helpful to define and distinguish two concepts: multidisciplinarity and interdisciplinarity. In a multidisciplinary collaboration, different professionals work on a common problem, interacting with each other but each contributing from within a defined disciplinary framework. The convening power of public health, in bringing people together and developing a shared sense of purpose and ownership, can be very fruitful in a multidisciplinary project. An example is the joint effort to identify and implement of a research agenda related to the discovery of the HFE gene and to develop education and guidelines for clinicians related to diagnosis of HFE-associated hemochromatosis (Appendix 1.2).

To achieve the novel integration or synthesis required in public health genomics, however, Bellagio participants identified the need to move further, toward an interdisciplinary collaboration, in which questions are framed and addressed jointly by persons trained in the different component disciplines. The need for such integration is apparent in debates about the contributions of ELSI research.

Integrating ELSI into the evaluation process

Workshop participants considered many issues evaluated in ELSI research as relevant to public health genomics, including the privacy of genetic information, the potential for genetic discrimination, both positive and negative, stigmatization and negative psychological consequences potentially arising from some genetic tests, the regulation of genetic tests, the governance of genomic research involving human subjects and/or human tissue (for example, population and patient-based biobank projects), the relationship between genetics and the concept of race, justice and equity in access to the benefits of genome-based research, and the use of genetic testing in the context of reproductive choice.

Participants concluded, however, that research addressing these issues often has little impact on efforts to improve population health. One problem is the tendency for the research to occur in isolation, because of the absence of an effective relationship between academic ELSI research and policy-makers and the separation of ELSI research from other scientific and clinical spheres. The promotion of interdisciplinarity would increases the potential for ELSI research to make constructive contributions.

Another problem is the frequent use of genetic exceptionalism as a frame for issues related to genetics and genomics. Bellagio workshop participants, in accord with a multidisciplinary group convened by the European Commission,⁴³ fa-

vored moving away from genetic exceptionalism. Genetic determinants should be neither privileged nor unreasonably demonized.³⁰ As an example, the widespread use of Huntington's disease – a highly-penetrant and fatal late-onset condition for which no effective treatment exists – as a paradigm for predictive genetic testing should be actively discouraged, as it gives a highly misleading idea of the predictive power of genetic information for most people. Examples drawn from common diseases, such as the genetic contributors to venous thrombosis,^{19,20} Alzheimer Disease,¹⁷ and other common disorders of public health significance^{10,14} are more readily generalizable.

Normalizing genetics as a contributor to risk, and as a result, achieving more balanced public dialogue, will enable a more rational approach to the use of genetics to benefit population health. At the same time, some of the debate surrounding genetics has pointed to the need for more adequate regulation and protection in other areas of biomedical research and clinical practice.

MAKING USE OF KNOWLEDGE INTEGRATION

The integrated multidisciplinary knowledge generated from an effective public health genomics enterprise supports four core activities (Fig. 1):

- Informing public policy: Included in this activity are legal, philosophical and social analyses, development of regulatory frameworks, engagement in the policy-making process, promoting relevant research, seeking international comparisons, and working with governments and relevant public institutions.
- Developing and evaluating preventive and clinical health services: This activity includes strategic planning; service organization, manpower planning and capacity building; service review, assessment and evaluation; and guideline development.
- Communication and stakeholder engagement: Relevant activities include promoting general genetic literacy in society, public dialogue, and engaging with industry, which is seen as a key player in the development of new genomicsbased clinical interventions.
- Education and training: This will involve promoting genetic literacy for health professionals, specific training for public health genetics specialists, and development of educational materials, courses, workshops and seminars.

Educational programs in public health genetics/genomics are already underway at some centers (Appendix 1.3). These efforts provide essential preparation for the multidisciplinary work envisaged for the translation of genome-based research into actions for population health, and serve as another important area for collaboration. There is a need to develop and disseminate competencies for public health genomics, which will differ substantially from competencies already developed, by NCHPEG and others, for genetics education in specific clinical fields.

This conceptual framework for public health genomics recognizes the importance of applied and translational research in achieving the goal of improving population health. Research activities inevitably identify gaps in the knowledge base that need to be addressed by further basic research (Fig. 1). The boundaries between basic and applied research are indistinct, and the continuum from research to practice may be better represented by the term "frontier research" proposed in a recent European public report.44 The dynamic and interactive nature of the enterprise is represented by double-headed arrows (Fig. 1): It is informed by societal priorities,45 generates knowledge as well as using it, and is modulated by the effects of its own outputs and activities. Thus, public health genomics incorporates a cycle of analysis-strategyaction (implementation)-evaluation, a widely recognized approach in public health practice. This cycle, which is equivalent to the US Institute of Medicine's cycle of assessment-policy development-assurance,46 describes how the enterprise carries out its activities.

AN INTERNATIONAL PUBLIC HEALTH GENOMICS NETWORK

After laying the groundwork describing the components of the public health genomics enterprise, the Bellagio workshop participants unanimously agreed to establish an international forum to address the global challenge for integrating and using genome-based knowledge and technologies for the benefit of population health. The forum will be known as the Genomebased Research and Population Health International Network or GRAPH Int. The use of the term Int signifies that the collaboration is not only international but also interdisciplinary and integrated. GRAPH Int is an international collaboration that facilitates the responsible and effective translation of genomebased knowledge and technologies into public policies, programs and services for the benefit of population health. Membership of GRAPH Int is open to all individuals and organizations that have an interest in this mission. Six initial goals for GRAPH Int were defined:

- 1. To provide an international forum for dialogue and collaboration
- 2. To promote relevant research
- 3. To support the development of an integrated knowledge base
- 4. To promote education and training
- 5. To encourage communication and engagement with the public and other stakeholders
- 6. To inform public policy

GRAPH *Int* will provide a concerted global approach to build the infrastructure that will be needed for the translation of developments in genome-based research into effective interventions to improve population health. International consensus has been reached on the scope and strategy for this enterprise. GRAPH *Int*, a new international forum and network, welcomes all those who wish to participate in this enterprise and invites them to work together to achieve its goals. A coordination and communication hub will be provided by the Public Health Agency of Canada.⁴⁷ The first meeting of this inter-

July 2006 · Vol. 8 · No. 7

Burke et al.

national forum occurred at the International Genomics and Public Health meeting in Montreal, Canada, June 4–7, 2006.⁴⁸

In summary, while the Human Genome Project and advances in molecular biology have forever changed the face of science, application of these scientific discoveries for the benefit of population health is a major challenge worldwide. We hope that the implementation of the public health genomics enterprise around the world facilitated by the newly formed international network could over time begin to harness genome-based sciences and technologies for the benefit of population health in the 21st century.

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References

- Collins FS. Shattuck lecture-medical and societal consequences of the Human Genome Project. N Engl J Med 1999;341:28–37.
- Roses AD. Pharmacogenetics and drug development: the path to safer and more effective drugs. Nat Rev Genet 2004;5:645–656.
- Austin CP. The impact of the completed human genome sequence on the development of novel therapeutics for human disease. *Annu Rev Med* 2004;55:1–13.
- Nelson HD, Huffman LH, Fu R, Harris EL. 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 Intern Med 2005;143:362– 379.
- Weinshilboum R. Thiopurine pharmacogenetics: clinical and molecular studies of thiopurine methyltransferase. *Drug Metab Disp* 2001;29:601–605.

- Higashi MK, Veenstra DL, Kondo LM, Wittkowsky AK, et al. Association between CYP2C9 genetic variants and anticoagulation-related outcomes during warfarin therapy. JAMA 2002;287:1690–1698.
- Rieder MJ, Reiner AP, Gage BF, Nickerson DA, et al. Effect of VKORC1 haplotypes on transcriptional regulation and warfarin dose. N Engl J Med 2005;352:2285–2293.
- Emens LA. Trastuzumab: targeted therapy for the management of HER-2/neuoverexpressing metastatic breast cancer. Am J Ther 2005;12:243–253.
- Krause DE, Van Etten RA. Tyrosine kinases as targets for cancer therapy. N Engl J Med 2005;353:172–187.
- Holtzman NA, Marteau TM. Will genetics revolutionize medicine? N Engl J Med 2000;343:141–144.
- Dipple KM, McCabe ER. Modifier genes convert "simple" Mendelian disorders to complex traits. *Mol Genet Metab* 2000;71:43–50.
- 12. Beutler E. Discrepancies between genotype and phenotype in hematology: an important frontier. *Blood* 2001;98:2597–2602.
- 13. Hubbard R, Lewontin RC. Pitfalls of genetic testing. N Engl J Med 1996;334:1192-1194.
- 14. Vineis P, Schulte P, McMichael AJ. Misconceptions about the use of genetic tests in populations. *Lancet* 2001;357:709–712.
- World Health Organization. The world health report 2003 shaping the future. Available at: www.who.int/whr/2003/en/index.html. Accessed January 16, 2006.
- Neuhausen SL. Ethnic differences in cancer risk resulting from genetic variation. Cancer 1999;86:2575–2582.
- 17. Mayeux R, Schupf N. Apolipoprotein E and Alzheimer's disease: the implications of progress in molecular medicine. *Am J Public Health* 1995;85:1280–1284.
- Roberts JS, Barber M, Brown TM, Cupples LA, et al. Who seeks genetic susceptibility testing for Alzheimer's disease? Findings from a multisite, randomized clinical trial. *Genet Med* 2004;6:197–203.
- 19. Reich LM, Bower M, Keys NS. Role of the geneticist in testing and counseling for inherited thrombophilia. *Genet Med* 2003;5:133–143.
- Christiansen SC, Cannegieter SC, Koster T, Vandenbroucke JP, et al. Thrombophilia, clinical factors, and recurrent venous thrombotic events. *JAMA* 2005;293: 2352–2361.
- 21. Marteau TM, Lerman C. Genetic risk and behavioural change. BMJ 2001;322:1056-1059.
- Audrain J, Boyd NR, Roth J, Main D, et al. Genetic susceptibility testing in smokingcessation treatment: one-year outcomes of a randomized trial. *Addict Behav* 1997; 22:741–751.
- McBride CM, Bepler G, Lipkus IM, Lyna P, et al. Incorporating genetic susceptibility feedback into a smoking cessation program for African-American smokers with low income. *Cancer Epidemiol Biomarkers Prev* 2002;11:521–528.
- Slattery ML, Edwards SL, Ma KN, Friedman GD. Colon cancer screening, lifestyle, and risk of colon cancer. *Cancer Cause Control* 2000;11:555–563.
- Mandelson MT, Curry SJ, Anderson LA, Nadel MR, et al. Colorectal cancer screening participation by older women. *Am J Prev Med* 2000;19:149–154.
- Madlensky L, Esplen MJ, Gallinger S, McLaughlin JR, et al. Relatives of colorectal cancer patients: factors associated with screening behavior. *Am J Prev Med* 2003;25:187–194.
- Ramji F, Cotterchio M, Manno M, Rabeneck L, et al. Association between subject factors and colorectal cancer screening participation in Ontario, Canada. *Cancer Detect Prev* 2005;29:221–226.
- Slattery ML, Kinney AY, Levin TR. Factors associated with colorectal cancer screening in a population-based study: the impact of gender, healthcare source, and time. *Prev Med* 2004;38:276–283.
- Office of Genomics and Disease Prevention, Centers for Disease Control and Prevention. ACCE model system for collecting, analyzing, and disseiminating information on genetic tests. Available at: www.cdc.gov/genomics/gtesting/ACCE/fbr.htm. Accessed January 16, 2006.
- Murray TH. Genetic exceptionalism and "future diaries" is genetic information different from other medical information? In *Rothstien M ed., Genetic Secrets: Protecting Privacy and Confidentiality in the Genetic Era*. New Haven, Yale University Press, 1997.
- Gollust SE, Wilfond BS, Hull SC. Direct-to-consumer sales of genetic services on the Internet. *Genet Med* 2003;5:332–337.
- 32. Williams-Jones B, Corrigan OP. Rhetoric and hype: where's the 'ethics' in pharmacogenomics? *Am J Pharmacogenomics* 2003;3:375–383.
- 33. Berwick DM. Disseminating innovations in healthcare. JAMA 2003;289:1969-1975.
- Greenhalgh T, Robert G, MacFarlane F, Bate P, et al. Diffusion of innovations in service organizations: systematic review and recommendations. *Milbank Quarterly* 2004;82:581–629.
- 35. Genome-based Research and Population Health. Report of an expert workshop held at the Rockefeller Foundation Study and Conference Center, Bellagio, Italy, 14-20 April, 2005. Available at: www.cgkp.org.uk/webgroups/file_admin/secure_file. php?file_ID=616. Accessed January 16, 2006.
- Centers for Disease Control and Prevention. Human Genetic Epidemiolgy Network. Available at: www.cdc.gov/genomics/hugenet/default.htm. Accessed January 16, 2006.
- Derré M, Gourraud P-A, Larré J-M, Barnetche T, et al. Towards a meta-analysis of HLA region microsatellites, the MAMSat project. *Tissue Antigens* 2005;66:562.

- Gourraud PA, Mano S, Barnetche T, Carrington M, et al. A Integration of microsatellite characteristics in the MHC region: a literature and sequence based analysis. *Tissue Antigens* 2004;64:543–555.
- Public Population Project in Genomics (P3G). Available at: www.p3gconsortium. org. Accessed January 16, 2006.
- 40. Bell J. The new genetics in clinical practice. *BMJ* 1998;316:618–620.
- Fears R, Roberts D, Poste G. Rational or rationed medicine? The promise of genetics for improved clinical practice. *BMJ* 2000;320:933–935.
- Day IN, Wilson DI. Science, medicine, and the future: Genetics and cardiovascular risk. *BMJ* 2001;323:1409–1412.
- McNally E, Cambon-Thomsen A, Brazell C, Cassiman JJ, et al. The 25 recommendations on the ethical, legal and social implications of genetic testing. European Commission. EUR 21120 – Luxembourg: Office for Official Publications of the European Communities 2004. Available at: europa.eu.int/comm/research/conferences/2004/genetic/pdf/recommendations_en.pdf. Accessed January 16, 2006.
- 44. Harris WC, Martin B, Bonaccorsi A, Flensted-Jensen M, et al. Frontier research: a European challenge. European Commission. EUR 21619 Luxembourg: Office for Official Publications of the European Communities 2005. Available at: europa. eu.int/comm/ research/future/basic_research/documents_en.htm. Accessed January 16, 2006.
- Knoppers BM. Of genomics and public health: building public "goods"? CMAJ 2005;173:1185–1186.
- Beskow L, Khoury MJ, Baker T, Thrasher J. The integration of genetics into public health research, policy and practice: a blueprint for action. *Community Genet* 2001;4:2–11.
- 47. GRAPH Int. Genome-based Research and Population Health. Available at: www. graphint.org. Accessed January 16, 2006.
- International Genomics and Public Health. 4th Annual DNA Sampling Conference. Available at: www.cdc.gov/genomics/events/files/print/conf_dnasampling_June06. pdf. Accessed January 16, 2006.

Appendix 1.1: Examples of current initiatives in public health genetics/genomics

Centers

Office of Genomics and Disease Prevention, Centers for Disease Control and Prevention

www.cdc.gov/genomics

Carries out research and integration on how human genomic discoveries can be used to improve health and prevent disease. Established and coordinates the HuGENet (Human Genome Epidemiology Network) initiative.

Public Health Genetics Unit and Cambridge Genetics Knowledge Park

www.phgu.org.uk; www.cgkp.org.uk

Assesses advances in genetic science and their impact on health services and healthcare policy. The Cambridge Genetics Knowledge Park brings together researchers and policy analysts in science, public health, law, social sciences and philosophy.

Centers for Genomics and Public Health

www.sph.unc.edu/nccgph/

www.sph.umich.edu/genomics/

www.depts.washington.edu/cgph/

Established by collaboration between the US Centers for Disease Control and Prevention and the Association of Schools of Public Health, and located at the Universities of Michigan, Washington and North Carolina. The Centers contribute to the knowledge base, provide technical assistance to local, state, and regional public health organizations and develop and deliver training to the public health workforce.

Genomics, Health and Society

www.u558.toulouse.inserm.fr

A multidisciplinary research team in an epidemiology and public health research unit from the National Institute for Health and Medical Research (Inserm U 558) located within the Federative Research Institute on "health, society" at the University Paul Sabatier of Toulouse, France, including biologists, clinicians, geneticists, philosopher, lawyers, sociologists and economists and leading the "genetics and society" platform of the Toulouse Genopole.

Genomics Directorate of the Population Health Division, Western Australian Department of Health

http://www.population.health.wa.gov.au/Genomic/index.cfm Aims to facilitate the integration of genetics into all aspects of public health, policy and programs.

German Center for Public Health Genomics

http://www.public-health-genetics.org

A German think tank in the field of public health genomics operating on the national, European and international level. As an umbrella institution located at the University of Applied Sciences in Bielefeld, it aims toward the advancement of interdisciplinary translational research through various fields of science and the humanities interdisciplinary and interinstitutional long-term cooperation and exchange across the boundaries of established academic disciplines as well as between relevant stakeholders in the German healthcare system.

Resources

HumGen

www.humgen.umontreal.ca

An international database on the legal, ethical and social aspects of human genetics, HumGen developed as a collaboration between academia, government and industry by the Centre de Recherche en Droit Public at the University of Montreal. GDPinfo

www2.cdc.gov/genomics/GDPQueryTool/default.asp

A searchable database of all the documents available on the Office of Genomics and Disease Prevention website, including the HuGE Net database.

PHGU Genetics Policy Database

www.phgu.org.uk/policydb/index/html

A web database of literature on policy development for genetics in health services and healthcare.

Projects

Evaluation of Genomic Applications in Practice and Prevention (EGAPP)

www.cdc.gov/genomics/gtesting/egapp.htm

This project aims to develop a coordinated process for evaluating genetic tests and other genomic applications that are in transition from research to clinical and public health practice.

P3G Consortium Public – Population Project in Genomics www.p3gconsortium.org/

An international consortium to provide the international population genomics community with the resources, tools and know-how to facilitate data management for improved methods of knowledge transfer and sharing.

Canadian Program on Genomics and Global Health www.utoronto.ca.jcb/genomics/index.html

Promotes the use of genomics and biotechnologies to improve health in developing countries.

Burke et al.

HuGENet

http://www.cdc.gov/genomics/hugenet/default.htm

A global collaboration of individuals and organizations committed to the assessment of the impact of human genome variation on population health and how genetic information can be used to improve health and prevent disease.

PHGEN

http://www.phgen.nrw.de

The Public Health Genomics European Network (PHGEN) is an EU-funded project (No. 2005313) covering all EU Member States, Applicant Countries, and EFTA-EEA to promote and stimulate the countries' efforts by developing PHG and by supporting effective networking in this emerging field in order to reach sustainability.

Appendix 1.2: Public health action to evaluate proposed population screening for hereditary hemochromatosis

With discovery of the *HFE* gene in 1996 and the identification of *HFE* mutations as the primary cause of hereditary hemochromatosis, many experts identified *HFE* mutation testing as a model for genetic screening of adult populations. Public health leadership has played an important role in evaluating this potential intervention.

1997—Meeting convened in US by NHGRI and CDC to evaluate state of knowledge about *HFE* and hereditary hemo-chromatosis, resulting in:

- Consensus statement calling for more research on *HFE* mutation penetrance before screening
- Series of articles defining current knowledge and practice standards

1999—International jury incorporating expertise in medicine, epidemiology, health services, ethics and social sciences convened to develop evidence-based recommendations regarding screening for hemochromatosis, under auspices of CDC and EASL.

- Jury recommended against population screening in absence of research documenting outcome benefit
- Jury recommended that diagnosis of hereditary hemochromatosis be reserved for symptomatic patients (as opposed to asymptomatic patients identified by biochemical or DNA-based testing)

2000–04—Population-based study of screening for hereditary hemochromatosis in 100,000 subjects funded by NHLBI and NHGRI found that

- Penetrance of *HFE* mutations low (consistent with smaller studies from US, Australia and Europe)
- Symptomatic hereditary hemochromatosis are rare
- Other population-based reports from Europe and US confirm low penetrance of *HFE* genotypes

2004—Launch of a CDC website providing education about hereditary hemochromatosis for healthcare providers and the general public, with an emphasis on identification of early symptoms of hereditary hemochromatosis by healthcare providers and family-based screening.

Appendix 1.3: Educational initiatives in public health genetics/genomics

Examples of educational initiatives that recognize the multidisciplinary approach of public health genomics.

Genetics in Public Health Training Collaboration with liaisons to the Washington State Department of Health, the Centers for Disease Control and Prevention and the Health Resources and Services Administration. This collaboration includes the University of Washington, University of Michigan, University of Minnesota, University of North Carolina, University of Pittsburgh and Johns Hopkins University.

University of Michigan: Public Health Genetics Interdepartmental Concentration (PHGIC) Students obtain MPH, MS or PhD degrees in one of the five departments of the School of Public Health following a curriculum that includes introduction to basic science of genetics, genetics in epidemiology, ethical, legal and social issues and opportunities to gain practical experience through internships and independent studies.

University of Washington: Multidisciplinary program for Public Health Genetics in the context of law, ethics and policy. The academic component of the Public Health Genetics program (http://www.depts.washington.edu/phgen) consists of a two-year graduate program leading to a Master of Public Health (MPH) degree in Public Health Genetics, a graduate certificate program, and a graduate program leading to a doctoral (PhD) degree.

Public Health Genetics Unit, Cambridge

The Public Health Genetics Unit provides courses in public health genetics for the University of Cambridge medical undergraduate course in public health, Masters of Studies in Public Health and Master of Philosophy in Epidemiology. It provides six-month placements for public health specialists in training. These placements include an attachment to Cambridge Regional Genetics clinical and laboratory services and involvement in the full range of PHGU multidisciplinary work. The PHGU also provides shorter courses such as the five-day Genetics and Health Policy course, and has the facility for visiting fellowships and other shorter or longer attachments by arrangement.

Center for Genomics and Disease Prevention, Center for Disease Control and Prevention

The Center for Genomics and Disease Prevention (CGDP) has developed public health genomics competencies for the existing workforce. The competencies and the process used to develop them are summarized at the CGDP website (http://www.cdc.gov/genomics/training/competencies/default.htm). Competencies are defined for the entire public health workforce and for specific subsets, including leaders/administrators, clinicians, epidemiologists, health educators, laboratory workers, and environmental health workers.