Genome-based Research and Population Health

Report of an expert workshop held at the Rockefeller Foundation Study and Conference Centre Bellagio, Italy, 14–20 April 2005

Public Health Genetics

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1. Introduction

The Rockefeller Foundation's Bellagio Study and Conference Centre, Lake Como, Italy

Modern research in genetics and molecular biology, boosted by information emerging from the Human Genome Project, offers new opportunities for the promotion of population health. Benefits are anticipated through more effective personalised preventive care, disease treatments with better specificity, and innovative drug therapies[1].

Such is the volume and complexity of new genomic information that there is an enormous task of sifting and evaluation to identify beneficial interventions and ensure that they are effectively implemented. This will require an integrated multidisciplinary effort including epidemiological studies in multiple populations, and storage and interpretation of large amounts of genomic information, followed by investigation of the efficacy, cost and social acceptability of proposed new interventions. When results are encouraging, strategies will be needed for effective implementation within health services. Other disciplines, including law, philosophy, theology, ethics, political science, anthropology and sociology, can contribute to the analysis and development of social, legal and regulatory frameworks in which these advances can occur.

Over the last eight years, efforts to address this challenge have developed as a new field within public health, variously dubbed *public health genetics* or *public health genomics*[2,3]. Initiatives in public health genomics, varying in focus but with similar overall aims, have been taking shape in several countries, and have begun to have an impact [Box 1]. Knowledge resources have been developed at several locations, programmes of research and policy analysis have been initiated, and the expertise of those taking the approach of public health genomics has become influential in the advisory and policy-making framework of some countries.

2. The Bellagio initiative

Although the full benefits of genomic research will take time to develop, potential applications are emerging already. There is both a need and an opportunity to create an infrastructure now to ensure that new developments can be evaluated as they emerge, that robust but flexible regulatory policies are in place to maintain public confidence, and that the health professional workforce has the necessary education and training to be able to integrate new knowledge and interventions successfully into their practice. There is a need, too, to ensure that any benefits from developments in genomics are available not only to rich countries but also to those in the developing world.

With these challenges in mind, an expert meeting was convened with funding from the Rockefeller Foundation at their conference centre in Bellagio, Italy in April 2005. The aim of the meeting was to explore the possibility of establishing an international network to promote the goals of public health genomics, to share knowledge and resources, and to ensure equitable access to the benefits of genome-based knowledge by all, including those in developing countries.

Box 1. Examples of some current initiatives in public health genetics/genomics

Centres

Office of Genomics and Disease Prevention, Centers for Disease Control and Prevention
www.cdc.gov/genomics
Carries out research 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. 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.umich.edu/genomics/ depts.washington.edu/cgph/ www.sph.unc.edu/nccgph/
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 work force.

Genomics, Health and Society
genopole-toulouse.prd.fr/layout.php?page=home3&id=100&lang=eng www.ifr126toulouse.org/
www-toulouse.inserm.fr/srv/bmip/fdrech/unites/U558/cambon.html
A multidisciplinary research team in an epidemiology and public health research unit from the National Institute of Health and Medical Research, located at the University Paul Sabatier in Toulouse. Leads the 'Genetics and Society' platform of the Toulouse Genopole.

German Centre for Public Health Genetis
www.public-health-genetics.org
A German 'think tank' in public health genetics operating on a national, European and international level. Coordinated from the University of Applied Sciences in Bielefeld. Aims to advance interdisciplinary translational research and communication.

Genomics Directorate of the Population Health Division, Western Australian Department of Health
www.population.health.wa.gov.au/Genomics/index.cfm
Aims to facilitate the integration of genetics into all aspects of public health, policy and programmes

Resources

HumGen
www.humgen.umontreal.ca
An international database on the legal, ethical and social aspects of human genetics, developed as a collaboration between academia, government and industry by the Centre de recherche en droit public at the University of Montreal.

GDPinfo
www2a.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 HuGENet database

PHGU Genetics Policy Database
www.phgu.org.uk/policydb/index.html
A searchable web-based database of literature on policy development for genetics in health services and health care

Projects

Evaluation of Genomic Applications in Practice and Prevention (EGAPP)
www.cdc.gov/genomics/gtesting/egapp.htm
The 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

HuGENet
www.cdc.gov/genomics/hugenet/default.htm
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.

The meeting was attended by a multidisciplinary group of eighteen experts from Canada, France, Germany, the United Kingdom and the United States.

3. Key themes

The Bellagio meeting was the first opportunity for experts who work in different roles, institutions and countries, but who have begun in a variety of ways to consider the implications of genomic knowledge for population health, to come together to develop a shared understanding of this new field and agree on priorities for taking it forward at an international level. Six key questions were explored in discussions at the meeting:

- What are the fundamental concepts and scope of public health genetics/genomics?
- Can the prospects offered by 'personalised medicine' be reconciled with the population-level goals of public health?
- What are the key ethical, legal and social issues raised by advances in genomics and how can they be addressed most effectively?
- How can we develop a more effective strategy for collecting and evaluating information on proposed gene-disease associations and gene-environment interactions?
- How can different disciplines work together effectively to achieve shared goals?
- What competencies do health professionals need to enable them to implement the new type of medicine promised by developments in genomics?

3.1 Exploring the scope and concepts of 'public health genetics/genomics'

Genetics or genomics?

There was general agreement that the field of interest was not best described – or served – by the term 'public health genetics'. The word 'genetics' has multiple meanings: it can be synonymous with inheritance, it can mean the DNA-based programme that underlies biological development and function, or it can imply technologies based on manipulation of genetic material. To some it implies the current realm of clinical genetic services, focusing on highly-penetrant single-gene diseases and chromosomal disorders. To others it carries overtones of eugenics: the misguided promotion of selective breeding (sometimes by coercive means) to 'improve' the health of populations.

For these reasons there was a general – but not unanimous – preference for the term '*genomics*', which was taken to mean knowledge about the structure and composition of the human genome, the characteristics of genes, and how genes function together during the development and life of the organism. Genomics includes the study of human inherited genetic variation and its relationship with health and disease. It also includes an understanding of somatic genetic and epigenetic changes and their role in disease processes.

A potential problem with 'genomics' is that it is a term not well recognised or understood by non-scientists but this might paradoxically be an advantage, as it is unencumbered by negative historical connotations and may enable a fresh start in dialogue with the public.

Beyond 'genomics'


Tom Murray and Teresa Marteau

Although generally preferable to 'genetics', 'genomics' does not necessarily capture the full scope of the knowledge that will contribute to new developments in clinical medicine, and that therefore comes within the scope of the enterprise. Many other fields of '-omics' are developing, including proteomics and metabolomics, which attempt to assemble information on the full range of genomic products, their structures, functions and interactions. The discipline of bioinformatics has evolved to respond to the need to collect, store, marshal and make accessible the huge amount of data generated by work in all the '-omic' fields of research. Systems biology is emerging to develop ways of modelling and understanding the complex behaviour of whole cells and tissues, building up from a knowledge of their component molecules and molecular networks. The term '*genome-based*', rather than 'genomic', was thought to convey more fully the breadth of knowledge that is being amassed in all these fields.

Which genomes?

It was stressed that the human genome is not the only one of relevance to human health. Our genome interacts with those of a myriad other organisms, including plants and microbes, both in maintaining healthy body function and in many disease processes. An understanding of pathogen genomes, in particular, is elucidating the molecular and cellular processes of infection and of variation in human susceptibility to infectious diseases. We need, too, to emphasise the importance of human genetic/genomic diversity, as a valuable resource for the human species.

Both knowledge and technologies

Knowledge about the function of the genome will, it is hoped, help us to understand better how to keep the human body healthy and how to treat disease more effectively. A related outcome from genomic research has been the development of a new range of *technologies* that make use of the ability to manipulate the genetic material. These technologies include, for example, gene-based systems for drug delivery, and methods for simultaneous measurement of the expression of multiple genes. Such technologies, it was decided, also fall within the scope of the field of interest.

Public health or population health?

The field that has come to be known as public health genetics or public health genomics is distinguished by its focus on the health and health care of populations, rather than individuals. However, the term 'public health' has different definitions and connotations in different countries. In the UK, it is a very broad field that has an involvement in all aspects of health services and health care, including health service organisation and evaluation as well, for example, as health policy, infectious disease surveillance, health needs assessment and planning, and health promotion. In the United States the remit of public health is less broad: public health professionals do not have direct involvement in health service

organisation or delivery except in the case of state-run activities such as population screening programmes. In several countries, 'public health' has tended to acquire some negative connotations, implying poorly-resourced health care programmes for deprived communities.

For these reasons, it was decided that the broad scope of the enterprise was better conveyed by the term '*population health*'.

Conclusion

It was agreed that the scope and vision of the enterprise could be defined as:

The responsible and effective translation of genome-based knowledge and technologies for the benefit of population health.

3.2 The individual and the population

The prospects for targeted prevention

Genomic information applies essentially to the individual, and to a lesser extent to his or her close relatives. Many scenarios for the future impact of genetics on clinical medicine involve the development of 'personalised' treatment and preventive interventions, based on genetic characteristics. The population approach, by contrast, has traditionally focused on average or aggregated needs and responses, with health promotion messages stressing the universal benefits of lifestyle, screening or other health-related recommendations.

These observations suggest a tension between the concept of personalised medicine and the traditional goals of public or population health. Geoffrey Rose[4] pointed out that there are two ways of preventing disease: first, by directing preventive interventions at those individuals who are at the greatest risk; and second, by trying to reduce risk across the population as a whole. He showed that although targeting interventions at the high-risk group resulted in the largest absolute reduction in risk for those individuals, a greater overall reduction in disease could be brought about by achieving a small reduction in risk over the whole population.

Some have concluded from this analysis that the 'high risk' approach to prevention is not the proper course of action for interventions aimed at improving population health[5]. However the 'one size fits all' stance is at odds with people's observation that some individuals do not become ill despite indulging in unhealthy behaviours or failing to follow screening recommendations. A more nuanced approach that incorporates differences in individual susceptibility might offer additional opportunities for disease prevention[6].

Several challenges arise with this approach. Research findings so far suggest that information on risk alone has only a small effect on personal health behaviour[7]. The availability of an effective intervention is important, as is the individual's assessment of their ability to achieve behavioural change; this in turn is strongly dependent on their familial and social environment. There is also the danger that those identified as at lower genetic risk may be falsely reassured.

Yet universal and high-risk approaches to prevention are not mutually exclusive. It was agreed that it would be irresponsible not to explore the potential for individualised prevention that genomic research

may offer. Some argued that it would also be unethical, knowing as we do that universal messages may be ineffective or even harmful for some members of the population.

Family history as a bridge between the individual and the population

It was suggested that, although as yet we know very little about the relationship between genotype and disease susceptibility, we do already have a useful indicator of genetic risk in the form of family history information[8]. Indeed, family history is indicative not just of genetic risk but also of risk resulting from shared environmental/lifestyle factors. Research programmes are underway to quantify more precisely the relationship between family history and disease risk, and to determine whether risk stratification and prevention targeted on the basis of family history can lead to improved health outcomes[9]. Family history could, in a sense, be regarded as a 'bridge' between the individual and the population.

Population screening

Some population screening programmes for genetic conditions are already in place, notably newborn screening programmes and programmes for detection of carriers of autosomal recessive disorders. It was agreed that public health has a role in attempting to ensure that screening programmes, including those for genetic conditions, are only introduced when they fulfil certain criteria[10]. These include a requirement that the condition be a serious one, that the screening test is highly predictive and fully evaluated, that the consequences of both positive and negative test results are known, that an effective intervention and follow-up healthcare are available to all, that informed choice is assured, that counselling services are in place, that the economic costs of the programme have been assessed, and that there is a 'cultural understanding' of the condition and of attitudes to screening in the population.

Many existing or proposed population screening programmes for genetic conditions fall short of these criteria. For example, one study found that many babies affected by sickle cell disease are not receiving effective treatment in the United States, obviating the purpose of screening[11]. There is a general impression in clinical and public health circles that powerful patient advocacy groups and commercial interests are pressing for the introduction of screening programmes of unknown and doubtful clinical utility. Some proposed programmes appear to be driven by a research agenda, and implementation as a service is at best premature. Programmes that identify individuals affected by autosomal recessive conditions often also pick up unaffected heterozygous carriers; where screening is carried out antenatally or during childhood, there is no clear benefit to these individuals and the lack of informed choice presents an ethical problem[12,13].

Most of these shortcomings are not unique to screening programmes for genetic conditions. Nevertheless, they offer both an obligation and an opportunity for public health action to protect the interests both of individuals and of the population as a whole [Box 2].

Conclusions

Those with a role in seeking to improve population health have a responsibility to ensure that any proposed targeted preventive interventions, or population-level programmes for genetic conditions, are implemented only after careful assessment and evaluation. There is a need for public health leadership to promote public understanding; to inform health professionals; to weigh costs and benefits; to counteract over-selling and 'hype'; and to contribute effectively to policy development.

Box 2. Public health action to evaluate a proposed population screening programme: hereditary haemochromatosis

With discovery of the *HFE* gene in 1996, and the identification of *HFE* mutations as the primary cause of hereditary haemochromatosis, 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 haemochromatosis, 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 convened to develop evidence-based recommendations regarding screening for haemochromatosis, under auspices of CDC and EASL
- Jury recommended against population screening in absence of research documenting outcome benefit
- Jury recommended that diagnosis of hereditary haemochromatosis be reserved for symptomatic patients (as opposed to asymptomatic patients identified by biochemical or DNA-based testing)

2000-4 Population based study of screening for hereditary haemochromatosis in 100,000 subjects funded by NHLBI and NHGRI
- Penetrance of HFE mutations low (consistent with smaller studies from US, Australia and Europe)
- Symptomatic hereditary haemochromatosis rare

2004 Launch of CDC web site providing education about hereditary haemochromatosis for health care providers and the general public. Emphasis on identification of early symptoms of hereditary haemochromatosis by health care providers and a family tracing approach rather than population-based screening.

3.3 Ethical legal and social issues ('ELSI')

Assuring appropriate evaluation of genome-based interventions and technologies is fundamentally an ethical concern for those responsible for efforts to promote population health. This concern points to the need to measure all relevant outcomes of genome-based interventions, including social outcomes such as the potential for 'genetic discrimination', both positive and negative, and negative psychological consequences arising from genetic testing. Other ELSI concerns relate to process: assuring appropriate procedures for informed consent and protection of privacy in both clinical care and research, and the governance of genetic research involving human subjects and/or human tissue (for example, population biobank projects). Broader questions will also need to be addressed as genome-based interventions become available, including the relationship between genetic variation and the concept of race; justice and equity in access to the benefits of genetics; and the use of genetic testing in the context of reproductive choice.

From a discussion of these issues at the workshop, several broad problems emerged that, it was thought, may be hampering a constructive contribution of the 'ELSI' field to the goal of improving population health.

'Genetic exceptionalism'

The term 'genetic exceptionalism' refers to the belief that genetic information is fundamentally different from other types of personal medical information, and that therefore it merits special protection[14]. This view may derive from exaggerated claims about the predictive power of genetic information, which have been met by equally exaggerated warnings about the consequences of its misuse.

There was clear consensus that there is a need to move away from genetic exceptionalism so that genetic factors come to be regarded in the same way as any other determinants of health. Genetic determinants should be neither privileged nor unreasonably demonised. The challenge of genome-based

health care should be accurately characterised; thus, the widespread use of Huntington's disease – a highly-penetrant and fatal late-onset condition – as a paradigm for genetics in medicine should be actively discouraged as it gives a very misleading idea of the predictive power of genetic information for most people.


Bartha Knoppers and Ron Zimmern

'Normalising' the perception of genetics and, as a result, achieving more balanced public debate, will enable a more rational approach to the use of genetics to benefit population health. New ways of thinking about ethical questions may also enable a more balanced view to emerge. It was suggested that there is now a move away from an emphasis on the right of an individual to act exclusively in his own interests, and a need to develop new ethical principles for populations. Ideas of social altruism, solidarity and universality are coming to the fore, together with the concept of the right of an individual to choose to act for the public good[15]. Viewed in this light, genetic and genomic information may come to be seen as a valuable resource to be shared and used for the benefit of all, rather than a dangerous weapon that must be prevented from harming individuals.

The gap between ELSI research and policy solutions

Bellagio participants shared the impression that the ELSI 'project' has come to be seen, by some scientists and funders, as a bottleneck that slows and restricts beneficial scientific advances and may encourage 'knee-jerk' political responses to largely hypothetical problems. They suggested that this negative view may be the result of somewhat naïve initial expectations that academic research would lead seamlessly to practical policy solutions. A consideration of policy-making processes suggests, rather, that an explicit effort will be needed, involving public health professionals with expertise in the policy process, to use results of ELSI research to inform policy development.

There was agreement that the view of ELSI research as something tacked on to the end of the scientific agenda has not been helpful. For example, the ACCE framework for the evaluation of genetic tests separates scientific and clinical evaluation from consideration of the ethical, legal and social consequences of a test[16]. However, many 'ELSI' issues – such as people's psychological responses to genetic test information – are integral to the assessment of clinical utility; that is, whether a test or intervention leads to an improved health outcome.

It was agreed that it would be more constructive to take a problem-based approach, bringing together all the knowledge and insight, both scientific and non-scientific, needed to analyse a potential new development (for example, a population biobank project, or a genomics-based clinical intervention) and to work out a way forward. Some of the issues involved in achieving truly interdisciplinary working are discussed later in this report.

There is also a need for a more coherent and collaborative approach to empirical studies within the ELSI field, so that data can be used to draw valid general conclusions. This is particularly important for studies pertinent to the assessment of the clinical utility of genetic tests and interventions: the use of agreed measures for factors such as health-related behaviour, perceived risk and anxiety would allow synthesis of data across multiple studies. The HuGENet initiative (discussed below) is an excellent model for such a collaborative approach.

3.4 A concerted approach to human genome epidemiology

Over the last 10–15 years, genetic epidemiology has essentially been synonymous with gene hunting: the search for associations between specific genetic variants and disease. This, however, is only the first step towards using such information clinically. Information is also needed on the prevalence of variants of interest in different populations and on how specific genetic variants interact with each other and with environmental determinants to influence risk or the clinical characteristics of disease. Any genetic tests developed on the basis of this information require careful validation and evaluation.

Studies are ongoing in all of these areas but there is an enormous task to be accomplished in assembling all the information that is available, storing it in usable form and analysing it critically[17]. Most reported associations turn out to be false positives (a problem that is likely to worsen as high-throughput genotyping of the many sample collections available around the world gets underway) so there is a need for systematic review and meta-analysis of many studies both to clarify the likelihood that an association is real and to obtain a measure of its strength.

The HuGENet initiative

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An initiative called HuGENet (Human Genome Epidemiology Network) was set up in 1999 by the Office for Genomics and Disease Prevention (OGDP) at the US Centers for Disease Control and Prevention in Atlanta, USA, to begin to tackle this task[18]. HuGENet has grown into an international network currently comprising nearly 800 collaborators in 43 countries. HuGENet's core activities are information exchange (through its website at www.cdc.gov/genomics/hugenet/default.htm), training and technical assistance, knowledge base development and information dissemination. A series of 42 HuGE reviews has been published. Each review identifies human genetic variations at one or more loci, describes what is known about the frequency of these variants in different populations, identifies diseases that these variants are associated with, summarises the magnitude of risks and associated risk factors, and evaluates associated genetic tests. Reviews point to gaps in existing epidemiological and clinical knowledge, thus stimulating further research in these areas.

It has become clear that genetic epidemiology needs a robust bioinformatic infrastructure to support this work. Projects are underway at both OGDP in Atlanta and the Public Health Genetics Unit (PHGU) in Cambridge to develop new systems for capturing and storing the relevant data in an appropriate format for use in meta-analysis and systematic review.

The structure of HuGENet is currently being revised along the lines of the highly successful international Cochrane Collaboration. Coordinating centres are being developed in Cambridge, Ottawa and Ioanina and an international steering committee for the network has been established. Several international consortia have been set up to work together on specific diseases such as Parkinson's disease and oral cleft; 24 such network 'hubs' have been established so far. HuGENet is becoming, in effect, a network of networks.

Building on the HuGENet model

Participants at the meeting agreed that HuGENet was both a useful model for how an international population health genomics network might operate, and a key associate of such a network. About half of HuGENet's members come from disciplines other than epidemiology, suggesting that there is broad multidisciplinary interest in the goal of using genomic information for population health.

Other disciplines and initiatives might benefit from taking a HuGENet-like approach. For example, as discussed above, the field of health psychology suffers from a lack of standardised methodology, hampering the comparison of different studies. Genetic test evaluation is also being approached piecemeal throughout the world, with initiatives currently underway under the auspices of both the European Union and the Organisation for Economic Cooperation and Development, as well as in many individual countries including Canada, the UK and the US. There is a need to bring these activities together so that expertise can be shared and wasteful duplication avoided; the proposed international network could potentially take on a coordinating role.

3.5 Working towards interdisciplinarity

Informal discussions in the meeting room

Knowledge and insight from many disciplines will be needed to achieve the goal of harnessing genome-based knowledge and technologies for the benefit of population health. Achieving this integration will not be easy. 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. Researchers in different disciplines are often physically separated in different departments or institutions and do not know or communicate with each other. Research findings are generally published in specialist discipline-based journals, and papers refer only to other work within that discipline; relevant information from other sources is not explored.

Multidisciplinarity and interdisciplinarity

It may be helpful, in thinking about how different disciplines might work together more productively, to define and distinguish two concepts: multidisciplinarity and interdisciplinarity[19,20]. In a multidisciplinary collaboration, different professionals work on a common problem and communicate with each other but each keeps their own professional 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 [Box 3]. This approach also has the advantage that the contribution of each person or group can be evaluated by criteria accepted by that discipline, and so is congruent with current modes of academic assessment and career progression. It may, however, be difficult to achieve a truly novel integration or synthesis of the knowledge emerging from such a project.

An 'interdisciplinary' collaboration integrates both the knowledge and the modes of thinking of the component disciplines and, ideally, leads to a synthesis that produces new knowledge. Such collaborations can be immensely productive and lead to innovative outcomes but there are many problems to be overcome, including a lack of shared values among the different disciplines involved, lack

of a framework for evaluating interdisciplinary work, and institutional constraints such as conventional discipline-based organisations that do not value or reward interdisciplinary work. Interdisciplinary projects may also fail if they are directed in a 'top-down' way, for political reasons, rather than arising from a perceived need among professionals themselves for a different way of tackling complex problems. Indeed, the personalities of those involved in interdisciplinary projects are an important factor in their success: some people relish the opportunity to transcend the boundaries of their discipline, while others do not.

New approaches are needed for assessing the impact or success of interdisciplinary projects, including measures of the process of interdisciplinarity itself, and the degree to which it has added value. It may be helpful to include a consideration of appropriate assessment criteria as part of the development of the project itself.

Box 3. From genomic research to clinical application: a multidisciplinary approach

New technologies are increasingly able to make a precise diagnosis of genetic abnormalities that underlie learning disability. Some, such as MLPA (multiplex ligand-dependent probe amplification) are now used to screen telomeres and so detect sub-microscopic deletions or duplications of genetic material at the ends of the chromosomes, areas that are particularly gene rich. As well as the technical evaluation, which tells us how good these new tests are at detecting abnormalities, there are many other questions in the area of learning disability that need to be considered if services to be provided that benefit individuals, their families and the population at large. Some of these have been addressed by a multidisciplinary group at the Cambridge Genetics Knowledge Park, working with wider groups of clinicians, researchers, parents and voluntary groups.

Specific areas of work have included:

- What is the value in psychological and social terms to patients and their families and carers of a genetic diagnosis? Does a genetic diagnosis help them to gain access to services? How can they best be supported during the processes of genetics referral, testing and subsequently coming to terms with a genetic diagnosis or failure to make a diagnosis?
- The development of evidence-based guidelines for clinicians who are not genetics specialists to undertake the best programme of investigation and referral for their patients. What information and educational support do they need?

Bringing together developments in science and technology with clinical, sociological and public health disciplines will improve practice in this area of health care.

Implications for an international network

Sometimes, a successful multidisciplinary or interdisciplinary project leads to the creation of a new discipline, as a group working together acquires a shared history that leads to a new sense of identity. It was felt that such an outcome might in due course emerge from the establishment of a network based on population health genomics. The group could develop new strategies for working across disciplines and widen the appeal of the enterprise which, despite the broad view that public health practitioners take of their field, may appear exclusive to others. It would be important for the network not just to develop a shared vision within itself, but actively to seek the involvement of the wider community.

3.6 Education and training needs

In the future, virtually all health professionals will need to have a working knowledge of those aspects of genetics that will directly affect their clinical practice. Many surveys have found that health professionals currently lack the necessary knowledge and skills[21]. A strategy for educating health professionals in

genetics has been published in the UK. Initiatives such as the National Coalition for Health Professional Education in Genetics (NCHPEG) in the US (www.nchpeg.org/), and the UK's National Genetics Education and Development Centre (www.geneticseducation.nhs.uk/), have begun to address the task of establishing the genetics competencies for different professional groups, ensuring that genetics is included in curricula, and developing suitable teaching resources.

Educational needs in population health genomics

It is also important that health professionals acquire some understanding of the broader, multidisciplinary concepts of population health genomics. A set of competencies in genomics for the US public health workforce has been developed by a multidisciplinary team convened by the OGDP (www.cdc.gov/genomics/training/competencies/default.htm). Competencies are documented for the public health workforce as a whole and for specific groups including leaders/administrators, clinicians, epidemiologists, health educationalists, laboratory staff, and environmental health workers.

In addition, some individuals will require an in-depth knowledge of this field[22], for example those involved in specialist commissioning, screening, preventive programmes, health service development and evaluation, and policy analysis and development. Leaders in specialist clinical fields will also need this more comprehensive understanding, in order to take the lead in promoting change within their own field and contributing to effective development of new services. Educational programmes in population health genomics are already underway at some centres [Box 4].

Box 4. Educational initiatives in population health genomics

Examples of educational initiatives that recognise the multidisciplinary approach of population 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://depts.washington.edu/phgen) consists of a two year graduate programme leading to a Master of Public Health (MPH) degree in Public Health Genetics and a graduate certificate program.

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 6-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 5 day Genetics and Health Policy course, and has the facility for visiting fellowships and other shorter or longer attachments by arrangement.

The role of an international network

It was seen as vital to develop a set of internationally agreed competencies for population health genomics. The proposed international network could take the lead in developing and disseminating these competencies, which will differ substantially from competencies already developed, by NCHPEG and

others, for genomics education in specific clinical fields. A suggested outline structure for competencies in population health genomics included knowledge and understanding in the areas of basic genomic/genetic science, human genome epidemiology, service delivery and organisation, genetic tests and their evaluation, public health policy, and the ethical, legal and social implications of genetic advances.

The proposed international network could also take the lead in developing resources for education in population health genomics. These resources should be dynamic and flexible, so that they can be tailored for the needs of different countries, languages and health care systems. A common web-based portal for sharing resources would be extremely useful though issues of intellectual property and ownership may need to be resolved.

All agreed that educational resources and programmes must be relevant to the needs of recipients. They should take a problem-based approach, putting population health genomics in the context of a medical or health service issue that is perceived to be important by the target audience. This approach will also enable ethical and social issues to be integrated into the teaching, avoiding the perception that they are a foreign or peripheral concern.

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The most efficient way of approaching an educational initiative on the scale that is envisaged is to take the approach of 'training the trainer' so that learning can be cascaded throughout a professional group. An international population health genomics network could explore ways of developing suitable programmes for educators in public health and other relevant fields, including making use of distance learning methods such as the World Wide Web and tele-medicine.

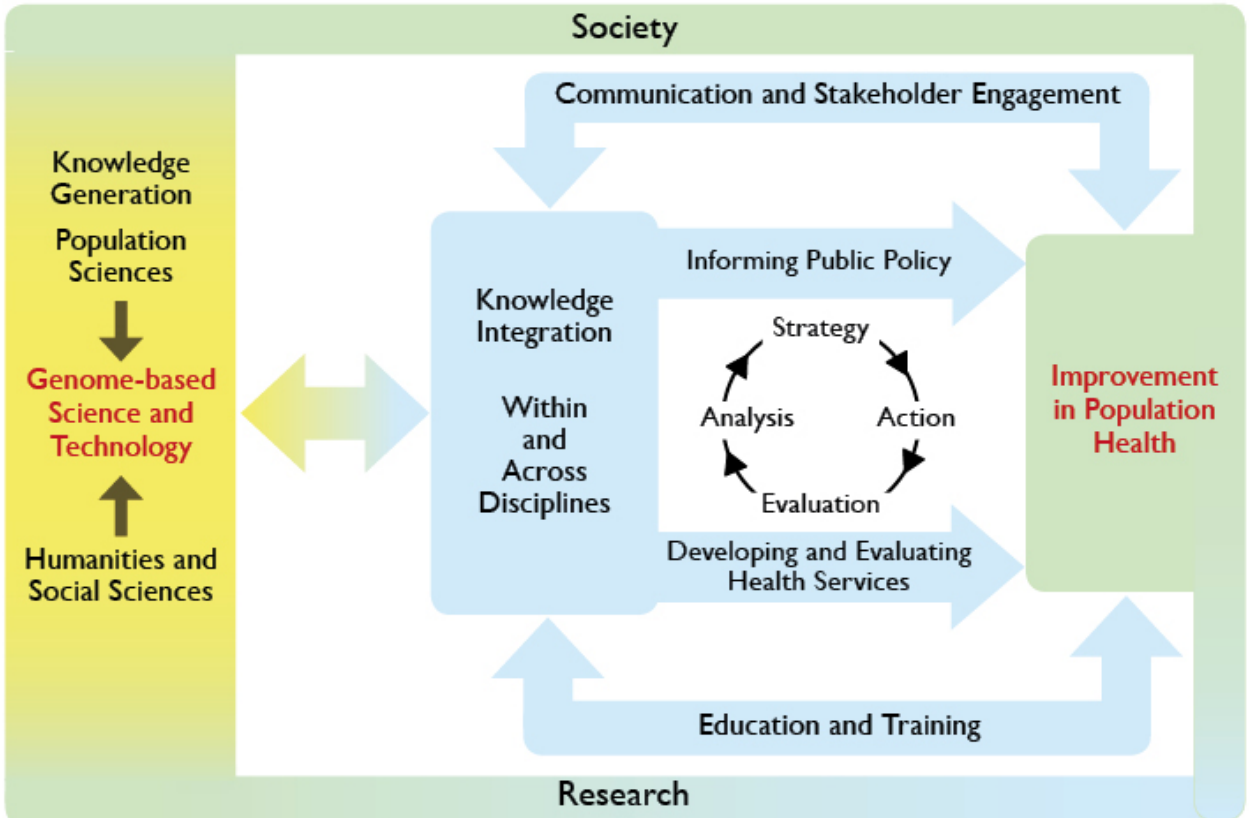
It will be important to develop and maintain links with other initiatives and networks for genetics education, such as NCHPEG and the recently-proposed European Coalition for Health Professional Education in Genetics (ECHPEG), in order to ensure that the core principles of population health genomics are included, at a basic level, in programmes developed for all health professionals. There will also be opportunities for sharing experience of successful methods and resources.

4. Developing the concept of the 'enterprise'

Building on the consensus that emerged from discussion of the six key themes, the workshop was able to develop an agreed concept for the '*enterprise*' of translating genome-based science and technology into improvements in population health. The expectation is that those engaged in the enterprise will take on a leadership role to promote its goals.

Figure 1 sets out this concept in visual form. The functions and activities shown in *blue* define the scope of the enterprise defined at the Bellagio meeting. The colour *yellow* represents the generation of knowledge through research; *green* represents all the activities, people, institutions and views that make up society in its widest sense.

Fig 1: The Enterprise



The enterprise embodies several key features:

1. The fundamental role of genome-based science and technology (highlighted in red). Any new development in modern genomics, or in molecular or cell biology, can legitimately come within the scope of the enterprise. The defining feature of the enterprise is that it is a way of working, or approaching problems, rather than a discrete subject that includes certain topics and excludes others.

2. The ultimate goal of achieving improvements in population health (also highlighted in red).

3. The need to incorporate research and knowledge from the population sciences and from the humanities and social sciences as relevant inputs to the enterprise. New knowledge is generated from research in these fields; the priorities for research are informed by, and negotiated with, the wider society.

4. The central role of knowledge integration, both within and across disciplines. This activity is the driving force or engine house of the enterprise. It is the process of selecting, storing, collating, analysing, integrating and disseminating information both within and across disciplines for the benefit of population health, and includes methodological development. It is the means by which information is transformed into knowledge.

5. The use of that integrated and interdisciplinary knowledge to underpin four core sets of activities used by the enterprise to effect improvements in population health:

   (a) *Informing public policy*. 'Policy' here includes a variety of public policies and programmes. Activities include legal, philosophical and social analysis at an applied level; development of regulatory frameworks; engagement in the policy-making process; promoting relevant research; seeking international comparisons; and working with governments.

   (b) *Developing and evaluating health services – both preventive and clinical*. This activity includes development of policies, programmes and services in the health sector; strategic planning; service organisation, manpower planning and capacity building; service review and evaluation; and guideline development.

   (c) *Communication and stakeholder engagement*. Relevant activities include public dialogue; 'marketing' the enterprise; and engaging with industry, which is seen as a key player in the development of new genomics-based clinical interventions.

   (d) *Education and training*. This will involve promoting programmes of genetic literacy for health professionals and generally within society; specific training for public health genetics specialists; and development of educational materials, courses, workshops and seminars.

6. The importance of programmes of applied and translational research (blue, therefore part of the enterprise), which contribute to the goal of improved population health and also identify gaps in the knowledge base that need to be addressed by further basic research (yellow). It is acknowledged that the boundaries between 'basic' and 'applied' research are indistinct.

7. The dynamic and interactive nature of the enterprise (represented by double-headed arrows): it is informed by societal priorities, generates knowledge as well as using it, and is modulated by the effects of its own outputs and activities.

8. The cycle of analysis – strategy – action (implementation) – evaluation, which represents a widely recognised approach to public health practice. This cycle, which is equivalent to the US Institute of Medicine's cycle of assessment – policy development – assurance, describes how the enterprise carries out its activities.

5. Establishing an international network: GRAPH *Int*

The Bellagio workshop unanimously agreed to establish an international forum to promote the enterprise of using genome-based knowledge and technologies for the benefit of population health. The forum will be known as the **Genome-based 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*.

Agreement was reached on the mission of GRAPH *Int*, its goals and membership criteria, and its initial priorities for action.

The mission of GRAPH Int

GRAPH Int is an international collaboration that facilitates the responsible and effective integration of genome-based knowledge and technologies into public policies, programmes and services for improving population health.

Membership

Membership of GRAPH *Int* is open to all individuals and organisations that have an interest in the development and use of genome-based knowledge for the benefit of population health.

Goals

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

Key tasks

Several early priorities were identified for GRAPH *Int*, while recognising the need for the network to be dynamic and flexible, particularly in its early stages. The workshop participants agreed to act as an interim Steering Committee for the network, and an interim Executive Group was appointed to oversee taking the work of GRAPH *Int* forward. The members of the interim Executive Group are:

Professor Wylie Burke	University of Washington, Seattle, USA
Dr Mohamed Karmali	Public Health Agency of Canada, Guelph, Ontario, Canada
Dr Muin Khoury	Office of Genomics and Disease Prevention, Centers for Disease Control and Prevention, Atlanta, USA
Professor Julian Little	University of Ottawa, Ottawa, Canada
Dr Ron Zimmern	Public Health Genetics Unit, Cambridge, UK

A possible location for an administrative hub for the network was identified; the expectation is that the institution hosting the administrative hub will also provide facilities for setting up and maintaining a website for GRAPH *Int*.

Working groups were set up to undertake initial key tasks identified for GRAPH *Int*:

(a) addressing the need to achieve more effective integration within the ELSI field and between ELSI work and other parts of the enterprise
(b) defining the research needs of the enterprise and working to inform the priorities of major funders
(c) addressing the education and training needs for public health
(d) identifying and prioritising other organisations that GRAPH *Int* may wish to form links with, and defining relationships with existing networks and organisations.

In recognition of the need to ensure effective participation of the developing world in GRAPH *Int*, an early priority was the establishment of links with relevant officials at the World Health Organisation and the leaders of the Canadian Program on Genomics and Global Health.

The goals of the enterprise and the role of GRAPH *Int* will be promoted through wide dissemination of the conclusions from the Bellagio workshop and by working to include the theme of genomics and population health in both national and international conferences.

6. Conclusions

The time is ripe for a concerted 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.

The Bellagio workshop participants

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Workshop participants

Organisers

Dr Ron Zimmern, Director, Public Health Genetics Unit, Cambridge, UK
Dr Ron Zimmern was appointed Director of the Public Health Genetics Unit in Cambridge in June 1997. He is also the Director of the Cambridge Genetics Knowledge Park (from April 2002) and the Institute of Public Health at the University of Cambridge (from January 2003). He is an Associate Lecturer at the University of Cambridge, a Consultant in Public Health Medicine at Addenbrooke's Hospital and a Senior Associate at the Judge Institute of Management Studies. He is Chairman of the Diagnostic and Screening Panel of the UK's Health Technology Assessment programme, serves on the Genetics Commissioning Advisory Group and the Steering Group for the National Genetic Testing Network at the Department of Health, and is on the Council for the British Society of Human Genetics. In addition to public health genetics, his interests include strategic planning, the relationship between clinical services and teaching and research, priority setting in the NHS , and the law and ethics of medicine.

Professor Wylie Burke, Professor and Chair of the Department of Medical History and Ethics, University of Washington, Seattle, USA
Dr Wylie Burke is Professor and Chair of the Department of Medical History and Ethics. She has adjunct appointments in the departments of medicine and epidemiology. Dr Burke is a faculty member in the Public Health Genetics Program and in the Medical Genetics Training Program. In 1994 she became the founding director of Women's Health Care Center at UW Medical Center-Roosevelt and served in that role until 1999. She has also previously served as associate director of the Internal Medicine Residency Program. Dr. Burke's research is focused on clinical and public health application of genetic information. Her work addresses the social, ethical and policy implications of genetic information, including the development of practice standards, public and professional education, genetic screening, and the impact of genetic counselling on risk perception.

Dr Muin Khoury, Director, Office of Genomics & Disease Prevention, Center for Disease Control and Prevention, Atlanta, USA
Dr Khoury is the first Director of the CDC's Office of Genomics and Disease Prevention. The Office was formed in 1997 to assess the impact of advances in human genetics and the Human Genome Project on public health and disease prevention. As the nation's prevention agency, CDC's mission is to protect the health and safety of people, to provide credible information to enhance health decisions, and to promote health through strong partnerships. CDC's Office of Genomics and Disease Prevention serves as the national focus for integrating genomics into public health research and programs for disease prevention and health promotion. Dr Khoury joined CDC as an Epidemic Intelligence Service Officer in 1980 in the Birth Defects and Genetic Diseases Branch, and as a medical epidemiologist in 1987. In 1990, he became Deputy Chief of the same Branch. In 1996, Dr Khoury chaired a CDC-wide Task Force on Genetics and Disease Prevention and provided important leadership in outlining a plan delineating the future direction that CDC should take in this important area.

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