

Public health genomics: origins and basic concepts

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Abstract

Knowledge and technologies arising from the Human Genome Project promise in time to offer new opportunities for the treatment and prevention of disease. The enterprise of public health genomics aims to bridge the gap between advances in basic research and their responsible and effective implementation in clinical services and public health programmes. Public health genomics stresses the importance of understanding how genes and environment act together to influence health; avoiding genetic exceptionalism; appreciating the social and political context of genomic advances; and encouraging critical evaluation of proposed new tests and interventions. New international networks and collaborations are being established to develop public health genomics and further its aims.

Key words: public health, genetics, genomics, prevention, genetic information, genetic tests

Introduction

New knowledge and technologies stemming from the Human Genome Project will in time have profound implications for medicine and health care. This much is commonly acknowledged, but there is still dispute about the timescales necessary for the translation of genomic science into effective and affordable interventions. A great deal of hype surrounds the science, and much has to be done to sort out the reality from the rhetoric. Public health genomics sets out to do just that. Its aim is to ensure that genomic knowledge and technologies are used responsibly to benefit population health. This paper sets out key concepts and explains the importance of this new field.

Definitions of public health genomics

A variety of definitions for public health genetics were developed, both in the US and in the UK, by its early practitioners. The UK built upon the Acheson definition of public health, which characterised public health as "*the art and science of promoting health and preventing disease through the organised efforts of society*". By extension, public health genetics was:

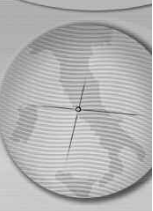
"The application of advances in genetics on the art and science of promoting health and preventing disease through the organised efforts of society".

Four points can be made about this definition. First, that the word 'genetics' was to be interpreted widely to encompass not only connotations of genetics as inheritance (such as in the term

'medical genetics', the specialty that deals with rare inherited disorders), but also 'genetics' as the science of DNA and all the molecular biology underlying development, normal physiology and disease. The need to convey this broader meaning for 'genetics', and also the understanding that multiple interacting genes contribute to risk for common chronic diseases, has led during the last few years to a trend towards replacing 'genetics' with the word 'genomics' - hence the move from 'public health genetics' to 'public health genomics' as the preferred terminology.

Second, that the ultimate aim of the discipline was to be the promotion of health and the prevention of disease. The term 'prevention' was to be interpreted widely and to include not only primary prevention (the prevention of disease initiation), but also secondary and tertiary prevention, the clinical measures used to delay disease progression and reduce disability. Third, that genetic science inevitably took place within a social and political context and that its influence on society would depend greatly on the policies adopted by its various institutions - not just scientific but governmental, legal, social and economic. And fourth, that its practice (as that of clinical medicine) was both an art and a science - that it required not just scientific, epidemiological and legal knowledge, but also a set of skills and competencies to create change and establish policies and services that would further its aims.

In recent years the discipline has blossomed, mainly through co-operation between centres in



Atlanta, Seattle and Cambridge UK, and groups in other countries engaged in programmes and activities related to the goals of public health genomics. In April 2005 an expert multi-disciplinary workshop funded by the Rockefeller Foundation and held at the Foundation's international study and conference centre in Bellagio, Italy was attended by 18 delegates from five countries (USA, UK, Canada, France and Germany). Its aims were:

1. To explore the possibility of establishing an international network to promote the goals of public health genomics
2. To share knowledge and resources
3. To ensure equitable access to the benefits of genome-based knowledge by all, including those in developing countries.

The meeting enabled a range of issues to be explored. At the meeting consensus was reached both on the scope and definition of public health genomics, and on the best way of moving its agenda forward at an international level. The Bellagio workshop unanimously concluded that public health genomics should be defined as:

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

The precise wording of the statement is important. The term 'genome-based' was chosen instead of either 'genetic' or 'genomic' in order to convey the full breadth of knowledge emerging not just from the human genome sequence but from research on the properties of its products and their functions in the human body. Genome-based technologies are important because they offer new modes of treatment and disease prevention, both in the developed and the developing world. The adjectives 'responsible' and 'effective' describe key attributes of the public health genomics approach: the need to ensure a solid evidence base for any new genome-based tests or interventions entering clinical or public health practice, and an insistence that this evidence base includes evidence of ethical and social acceptability, as well as the development of an appropriate regulatory and public policy framework. The Bellagio workshop in effect endorsed the need for an integrated, multidisciplinary approach that moved away from a tendency to view ethical, legal and social (ELSI) research as an optional extra tacked on to the end of the scientific or clinical agenda towards embracing it as an equally important partner in the endeavour to harness the fruits of genetic science "for the benefit of population health".

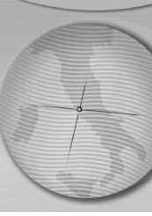
The terms 'public health genetics' and 'public health genomics' are now widespread, but the use

of the words 'public health' has led to some misunderstanding because of different interpretations of its subject matter in different countries. In some the words are used mainly in the context poorly-resourced health care programmes for deprived communities. In others, the scope of public health involvement in genetics may be largely limited to state-led initiatives such as newborn screening programmes that focus almost entirely on the inherited disorders, while in others again the term defines a broad sphere of action encompassing both the strategic planning and the organisation and delivery of health services.

In Europe, the term 'community genetics', has had a fairly wide following, mainly among medical or clinical geneticists. Its founder, Leo ten Kate, has described it as "bringing genetic services to the community as a whole" and says of it, "clinical genetics in itself is not community genetics, but making clinical services available to people in the community certainly is.... The distinction should be clear... The clinical geneticist is waiting in his consulting room for people to come to him... the community geneticist, however, is going out to the community, searching for people who may be at risk." [1]. In that sense therefore 'community genetics' concerns itself mainly with inherited or heritable single gene and chromosomal disorders and the application of the specialty of medical genetics in a community setting. Its scope may thus be conceptualised as a subset of 'public health genomics', which is a much broader and multifaceted discipline that additionally embraces complex disorders, a whole range of medical and surgical specialities, and the policies of political, legal and social institutions in society.

Genes and environment as determinants of disease

Since its inception, public health genomics has emphasised that both genes and environment must be explicitly included in models of disease causation. This emphasis represents a significant change from the traditional focus of public health practitioners on the social and environmental determinants of disease. Public health genomics has attempted to dispel the old 'nature versus nurture' debate, which is fundamentally flawed: both nature *and* nurture are always implicated in every human characteristic, including disease susceptibility, onset, progression and response to treatment. The 'nurture' (environmental) component comprises a complex array of determinants including social and political influences as well as obvious factors such as diet or environmental pollution. 'Genes' may be regarded



as 'internal' determinants, to be treated no differently analytically or methodologically from the more familiar external environmental factors commonly investigated by epidemiologists.

Genes and environment act together to cause disease but the emphasis of public health genomics is overwhelmingly on prevention of disease by altering modifiable environmental factors, not by intervention at the level of the genome. These two approaches to disease prevention have been termed, respectively, phenotypic and genotypic prevention. [2] Genotypic prevention has a place in some circumstances, for example as an option for a couple who are at risk of having a child with an inherited (Mendelian) disease. However reducing the incidence of common chronic disease, the aim of all public health practitioners, is only feasible by phenotypic prevention.

The holy grail of public health genomics is that it may be possible, once we understand both the genetic and the environmental factors involved in the causation of disease, and how they interact, to devise effective preventive interventions targeted at individuals with specific genotypes. Its primary endeavour would be thus directed not at technological advances such as gene therapy, the use of stem cells or nuclear transfer technologies - these have their place and may well be of huge importance for a small number of individual disorders or individual patients - but at sub-categorising populations according to the effectiveness of preventive environmental interventions in different population groups stratified according to genetic risk. This 'personalised' approach can be extended to individualised disease management as well as population prevention. For example, the study of pharmacogenetics aims to elucidate the relationship between genetic factors and response to medicines, so that drugs may be targeted at those most likely to respond and least likely to suffer adverse reactions.

The concept that disease arises as a result of the combined effects of genes and environment is a simple one but the task of understanding what all the relevant factors are, and how they work together, is far from simple. The reason is the sheer complexity of biological systems. Any biological process involves the participation of multiple genes, expressed in complex tissue-specific and temporal patterns under the influence of intricate control systems. These control systems are mediated by epigenetic mechanisms: chemical modifications to the gene that do not change its DNA sequence but affect its transcriptional activity and thereby its contribution to the

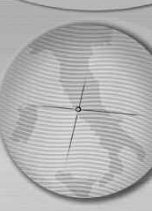
function of the cell. To these processes that operate at the level of genes must be added further layers of complexity at the level of gene products (hundreds of thousands of different proteins and other metabolites) intracellular signal transduction systems, cell-cell interactions and long-range influences such as circulating hormones. These molecular and cellular processes are susceptible, either directly or indirectly, to influences from the external environment.

In view of the considerable challenge that lies ahead in developing an understanding of how the genome works in health and disease, an important early role for public health genomics will be to counter the hype that accompanies much of genome based research and to stress the importance of ensuring that any new tests or interventions arising from genomic research are not introduced prematurely but are thoroughly evaluated and supported by a sound evidence base.

Genetic exceptionalism

The Human Genome Project - the sequencing of the complete DNA code - has understandably been accompanied by much excitement and many overheated predictions about an imminent 'revolution' in health care. These predictions have also aroused disquiet, however, because they imply that genomic information is exceptionally powerful - more powerful than other types of personal medical information - and therefore should have special protection. This argument is known as 'genetic exceptionalism'. [3] Concerns about the predictive power of genetic information have led in turn to anxiety about the possible misuse of this information to discriminate unfairly against individuals. Frequently, calls are made to outlaw the use of DNA test results for particular purposes, such as in the context of decisions about insurance or employment.

We believe that part of this anxiety is due to a failure to be clear about what we mean by the term 'genetic information', and in particular to distinguish between its meaning as 'information about an inherited disorder' and as 'information derived from the use of DNA and other genome-based tests'. [4,5] Diagnostic or predictive genetic tests for highly penetrant heritable conditions may have serious implications both for the individual who is tested and for his or her relatives. We accept the argument that there should be particular safeguards (such as the use of formal genetic counselling) when considering the use of tests in inherited disorders, or to ensure people with these diseases are not subject to unfair discrimination for any reason.



However we reject the view that the same arguments can be used in the context of genome-based tests generally or of common complex disorders. Genome-based tests may have diagnostic applications in common disease, for example to help distinguish different molecular subsets of a disease, which may require different treatment. They may also in the future be used in estimates of an individual's susceptibility to various diseases, in order to inform the use of preventive interventions. However, this information will be probabilistic in nature and will have minimal implications for other family members. Clarity of thinking is needed about the actual predictive power of DNA variants, which may on their own (outwith the classical inherited disorders) be less predictive of ill health than phenotypic biomarkers such as blood proteins and metabolites, or lifestyle factors such as smoking status or diet.

To the extent that arguments might be adduced to place constraints on the generation or use of risk based information, we suggest that to forbid the use of DNA-based risk information while placing no restrictions on other determinants of risk is illogical and unwarranted. Although genetic variants play a part in susceptibility to disease, they should not be either privileged or unreasonably demonised.

Priorities in Public Health Genomics

The practice of both public health and of clinical medicine must have regard to the knowledge derived from genetic and molecular science. An understanding of the cellular and molecular mechanisms of disease will be as important in the coming decades for the prevention of disease and the promotion of health as has been an appreciation of the importance of the social determinants of health in the last fifty years. Geneticists have, understandably, been reasonably receptive to this message, notwithstanding a lack of knowledge about what their public health colleagues actually do. Epidemiologists have also been reasonably quick to embrace the importance of genetic factors as health determinants and to include within epidemiological studies measurements of genetic variants.

The policy community have also, on the whole, taken on board (at least in countries such as the UK, continental Europe, the US, Canada and Australia) the importance of genetic science and biotechnology, both for the impact that it might have for the health of the population and for its economic benefit. National policies have

therefore been devised that stress the importance of genetics and molecular science research; the need for a vibrant research base and research capacity; the imperative of strong and well developed links between academia, health services and the commercial sector; the importance of appropriate and balanced regulatory regimes; and the growing importance of public health and preventive medicine.

By contrast, public health professionals have been less quick to appreciate the importance of genetic factors and how an understanding of genetic and molecular mechanisms might help in promoting health and preventing disease, tending in its stead to characterise genetic science as being only of relevance to clinical practice and to individual preventive care. We believe the intellectual challenge for the public health community is to gain a broad understanding of all the fields of knowledge that feed into the enterprise of public health genomics - genomic science, the population sciences, and relevant insights from the arts, humanities and social sciences and of the importance and implications of gene-gene and gene-environment interaction; and of being able to relate the relevance of this knowledge for both population and individualised preventive strategies.

At a practical level there is a need for leadership in public health genomics: to develop general 'genomic literacy' in the public health workforce, to build a cohort of specialists within public health and other professional groups who have a detailed understanding of the field, and to inform intelligent and evidence-based implementation of genome-based tests and interventions in health services.

The Practice of Public Health Genomics

The Bellagio workshop also developed a consensus view of how public health genomics was to be practised, an activity that we termed the 'enterprise'. This is represented by the darker areas in Figure 1. This vision for public health genomics can be found in more detail in a paper by the Bellagio participants published in the journal *Genetics in Medicine*. [6]

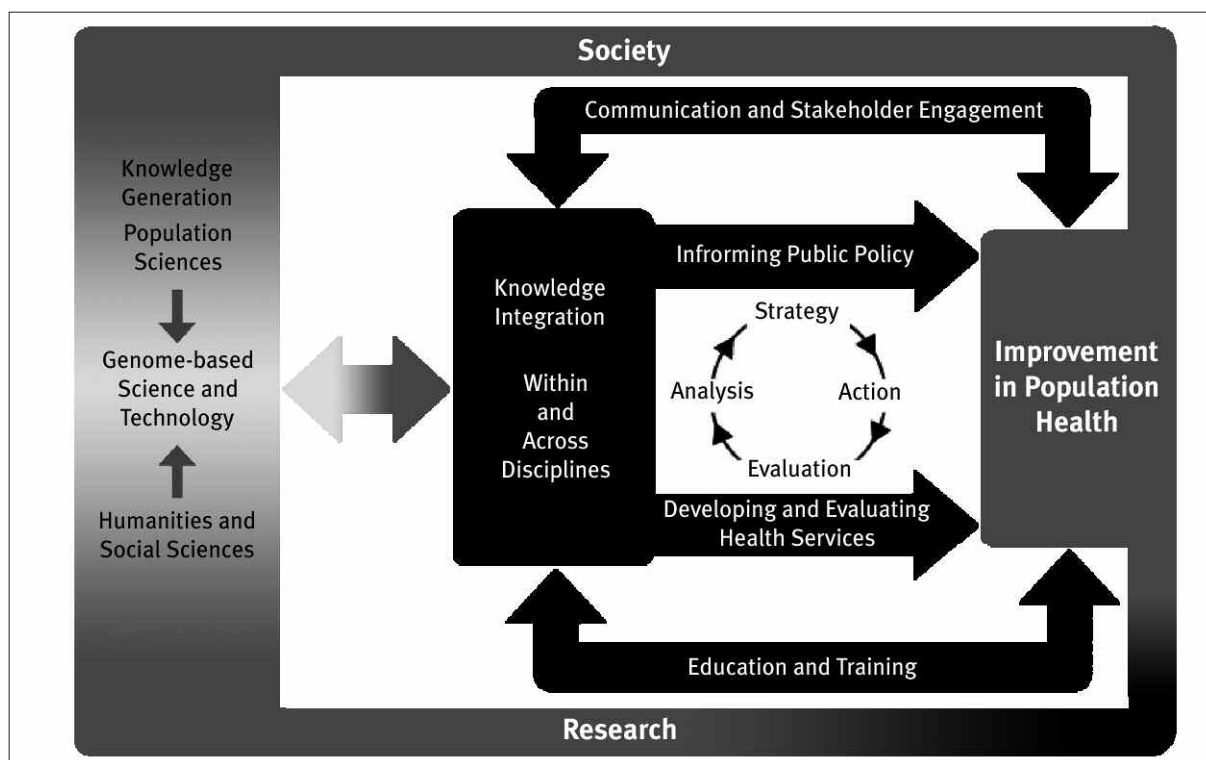
Public health genomics is still in an early phase of development. It has yet to reach 'critical mass' in any individual country. In many parts of the world it does not yet exist. Its further development demands that the pioneer groups and organisations work together to share resources and establish collaborations in key areas of work. To this end, the Bellagio group decided to set up an international network, to be known as the Genome-based

Research and Population Health International Network, or GRaPH *Int*. The term *Int* signifies that the Network is interdisciplinary and integrated as well as international. GRaPH *Int* was officially launched by the Chief Public Health Officer of Canada, Dr David Butler-Jones, at the 4th International DNA Sampling Conference: Genomics and Public Health, on 6 June 2006. Its

administrative hub is funded by the Public Health Agency of Canada. Its mission, echoing the Bellagio statement is that it is to be:

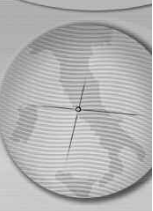
“an international collaboration that facilitates the responsible and effective integration of genome-based knowledge and technologies into public policies, programmes and services for improving population health”.

Figure 1. The Enterprise



Notes

- The input to the enterprise (on the left of the diagram; not generally forming part of public health genomics itself) is the research base, both in genome-based science and technology and also in the population sciences, the humanities and the social sciences. This is the phase of knowledge generation. The goal of the enterprise (on the right of the diagram) is benefit for population health.
- Information stemming from basic research is not usable on its own, but must be integrated, both within and across disciplines. Public health genomics begins with knowledge integration, defined as the process of selecting, storing, collating, analysing, integrating and disseminating information. This is the means by which information is transformed into knowledge, and is the driving force of the enterprise.
- The integrated knowledge base for public health genomics is used to underpin four core sets of activities:
 - Communication and stakeholder engagement (including, for example, public dialogue and involvement, and engagement with industry)
 - Informing public policy (including applied legal and policy analysis, engagement in the policy-making process, seeking international comparisons and working with government)
 - Developing and evaluating health services (including strategic planning, manpower planning and capacity building, service review and evaluation, and development of new programmes and services)
 - Education and training (including programmes of genetic literacy for health professionals and generally within society, specific training for public health genomics specialists, and development of courses and materials)
- The mode of working of public health genomics is described by the cycle of analysis—strategy—action—evaluation, which is a widely recognised representation of public health practice.
- Public health genomics does include a research component, shown at the bottom of the diagram. This is not basic research, but programmes of applied and translational research that both contribute directly to the goal of improving population health and also identify gaps in the knowledge base that need to be addressed by further basic research.
- Public health genomics does not operate in a vacuum. It is embedded within a social and political context, and informed by societal priorities.
- Double-headed arrows throughout the diagram indicate the dynamic and interactive nature of the enterprise: it generates knowledge as well as using it, and is modulated by the effects of its own outputs and activities.



GRaPH *Int* has set up a website [7] that provides details about the work of the network and a portal to sources of news and information about public health genomics. A full report of the Bellagio workshop [8] is also available on the GRaPH *Int* website.

In 2006, a similar network was established in Europe with funding from DG Sanco. It involves over 30 member states and is intended to bring to them an appreciation of the importance of public health genomics and to facilitate joint work between the public health and genetics communities within member states. The Public Health Genomics European Network (PHGEN) [9] is co-ordinated by the Landeinstitut für Öffentlichen Gesundheitsdienst (Logd) in Bielefeld, Germany. Its associate partners are the German Center of Public Health Genomics in Bielefeld, Germany and the Public Health Genetics Unit in Cambridge, UK. The aims and activities of PHGEN are discussed in detail in a paper by Brand in this issue.

Other activities relevant to public health genomics are also underway in Europe. EuroGentest [10] for example, is a European Union funded Network of Excellence that aims to improve the quality of genetic testing services in member states, including ensuring that appropriate regard is paid to issues such as ethical and social questions, health economic impact, and intellectual property rights. Other examples of partner programmes and organisations are listed in the introductory editorial in this issue.

The history of public health genomics

It might be appropriate to conclude with a short account of the development of public health genomics. The roots of the discipline as we now conceive it can be traced back to the mid-1990s, as the Human Genome Project gathered pace. In the United States, public health practitioners at the Centers for Disease Control and Prevention (CDC) in Atlanta were the first to make explicit moves to bring public health and genetics together. Muin Khoury's 1996 landmark paper in the *American Journal of Public Health* (*From genes to public health: applications of genetics in disease prevention*) [11] articulated the thinking behind the establishment of a CDC Task Force on Genetics and Disease Prevention. In turn, the Task Force's report *Translating advances in human genetics into public health action* [12] led in 1997 to the establishment of the Office of Genetics and Disease Prevention (OGDP) at CDC, under Khoury's leadership. OGDP has recently changed its name to the

National Office of Public Health Genomics. [13] The first annual conference on genetics and public health was held in Atlanta in 1997, attracting delegates from across the United States and internationally.

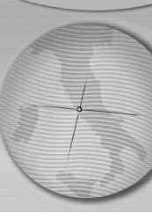
In the United Kingdom it was initially the genetics community that led the way, with two influential reports by an expert advisory group to Government in 1995. [14] These reports set out the potentially far-reaching changes to the country's National Health Service that would result from a growing understanding of the effects of normal genetic variation on susceptibility to disease, disease progression and response to treatment. Ron Zimmern was the first to take up the challenge these predictions raised for the public health community, setting up the Public Health Genetics Unit in Cambridge [15] in 1997.

The United States has, from the beginning, led the way in developing the discipline of public health genomics at an academic level. The first multi-disciplinary Masters' programmes in were established at the Universities of Washington and Michigan during the second half of the 1990s. [16] These programmes were developed and supported by faculty from a variety of academic departments including epidemiology and public health, medical ethics, law, pharmacy and social sciences, who also adopted a multi-disciplinary approach in their own research.

Since the turn of the millennium, public health genomics has acquired recognition and credibility through the publication of a growing body of scientific papers that have established the academic credentials of the field. Growing contacts between the groups in Atlanta, Seattle and Cambridge, and the engagement of others involved in relevant programmes, activities and collaborations around the world, has now led, through the Bellagio workshop and the establishment of GRaPH *Int*, to an international movement that will further consolidate the position of the discipline.

Conclusions

Public health practice in the 21st century can no longer ignore the knowledge derived from genetic and molecular science. An understanding of the molecular and cellular mechanisms of disease will be as important to the public health community of the future as an understanding of the social determinants of health. The political, ethical, legal and social contexts in which population health genomic science and technology are developed will be critically important. Practical advances will depend on



breaking down barriers: between the humanities and the sciences, between clinical and public health medicine, between concepts of genetic and environmental determinants of health, and between the basic and clinical sciences.

Challenges lie ahead for public health genomics, both intellectual and practical. Hype and rhetoric must be distinguished from reality; the complexities of biological systems must be appreciated; the dangers of genetic exceptionalism and genetic determinism must be avoided; the political and social context must be taken into account; and new technologies such as genetic tests must be critically and formally evaluated. Health professionals of all types and the general public must be prepared to understand the impact that our increased knowledge of biological systems will have on society. Public health genomics is intended to focus on these areas of concern and to provide independent knowledge and skills that will enable these matters to be responsibly and efficiently resolved. Progress towards this end can be accelerated by communication and collaboration. International networks such as GRaPH *Int* and PHGEN will help to bring the vision of using genome-based knowledge and technology for the benefit of population health closer to reality.

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