Extending the reach of public health genomics: What should be the agenda for public health in an era of genome-based and "personalized" medicine?

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Abstract: The decade following the completion of the Human Genome Project has been marked by divergent claims about the utility of genomics for improving population health. On the one hand, genomics is viewed as the harbinger of a brave new world in which novel treatments rectify known causes of disease. On the other hand, genomics may have little practical relevance to the principal causes or remedies of diseases which are predominantly social or environmental in origin, particularly in low- and middle-income countries. Those supportive of a role for public health genomics argue that increasing knowledge of genomics and molecular pathology could unlock effective diagnostic techniques and treatments, and better target public health interventions. To resolve some of these tensions, an international multidisciplinary meeting was held in May 2010 in Ickworth, United Kingdom, with the aim of setting an agenda for the development of public health in an era of genome-based and "personalized" medicine. A number of key themes emerged, suggesting a need to reconfigure both the focus for existing genomic research and the stage at which funding is targeted, so that priority is given to areas of greatest potential health impact and that translation from basic science to implementation is given greater emphasis. To support these developments, there should be an immediate, sustained and systematic effort to provide an evidence base. These deliberations formed the basis for six key recommendations, which could guide the practice of public health in an era of genomics and personalized medicine. ***Genet Med*** **2010:12(12): 785–791.**

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Knowledge of genetics and molecular biology has developed at an ever-increasing pace over the past decade, promising multiple opportunities for improving health. Yet, it remains unclear how public health professionals should engage with this scientific agenda. On a conceptual level, tensions may arise as the theoretical basis for traditional public health practice has been broadly collectivist in nature, while increasingly the thrust of much genomic medicine is to foster a narrower individualistic approach focused upon subpopulations and persons. Thus, a dual rhetoric has emerged both about the transformative power of "personalized" medicine to improve health at the level of the individual and the proper role of public health in that quest, as the role of public health includes the stratification of populations into groups rather than the provision of individualistic outcomes. The ability to distinguish between groups and individuals (on the one hand) and groups and whole populations (on the other hand) is likely to be critical in the future development of public health genomics and in targeting health interventions more generally.

A further claim is that advances in genomics and personalized medicine are of limited relevance to public health professionals on the basis that social determinants of health have greater population impact and are more malleable than genomic factors.[1] More prosaically, existing methods of priority setting within research and clinical care, together with wider ethical, economic and political factors, have thus far limited the possibilities for genomic advances to be applied within a public health setting especially in low- and middle-income countries (LMIC).

Given these concerns, our aims were to evaluate the relevance of genomics (including personalized medicine) for public health practice and to propose focused recommendations to enable public health practice to take advantage of the developments in genomics.[2]

PROCESS

A meeting of international experts from multiple disciplines was held in Ickworth, Suffolk, United Kingdom, from 10 to 14 May 2010 to reflect upon these aims. Experts in medical genetics, genomics, public health, ethics, social science, and law were drawn from Argentina, Australia, Canada, France, Italy, the Netherlands, Nigeria, United Kingdom, and the United States. The scope and methodology for this meeting drew upon a framework established by an earlier multidisciplinary expert meeting held in Bellagio, Italy, in 2005,[3] which had formulated a definition of public health genomics as "the responsible and effective translation of genome-based science and technologies for the benefit of human health."[4] The Bellagio meeting also articulated a model for the integration of knowledge within and across disciplines, which was deemed to be central to the effective translation of genome-based science and technology into improved population health, and established an international collaboration (GRAPH-*Int*—the Genome-based Research

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And Population Health International Network)[5] as a forum for fostering and developing public health genomics.

In the 5 years since the Bellagio meeting, our approach was also informed by a number of considerations that have emerged or gained greater emphasis: first, an explicit rejection of genetic exceptionalism: that is, rejecting the claim that all genetic and genomic samples and data merit special protection, regardless of their medical sensitivity or level of predictiveness[6]; second, an increasingly compelling need for a comprehensive evidence base to support the process of translation of scientific developments to benefit population health[7]; and third, an understanding that the use of genomic information and personalized medicine in the context of public health genomics implies a focus on the predictive, diagnostic and therapeutic outcomes for stratified populations and subpopulations rather than individuals.[8,9] A number of substantive issues emerged from the discussions.

THE POTENTIAL FOR GENOMICS TO IMPROVE POPULATION HEALTH

Over the past 5 years, much research has focused on genomics with a view to identifying the contributions of different genetic variants to the pathology of disease (particularly common complex diseases) and thus to develop strategies for both predicting and preventing diseases or ameliorating their effects.[1] There is little doubt that genomic research will provide an important foundation for understanding biological disease mechanisms which may, in the longer term, lead to effective and useful clinical and public health interventions (including new biomarkers, therapeutic agents, and vaccines). Understanding how different genetic variants contribute to the phenotypic development of disease, or how stratification of a population by genetic risk could enable the targeting of preventive measures toward those at highest risk, could prove to be enormously valuable.[10]

However, despite considerable investment to date, the findings from such research have been modest and have failed to result in immediate or direct benefits for population health. The lack of results has been compounded by artificially raised expectations in the minds of some commentators, which has generated some disillusionment and cynicism.[11] This lack of progress is due to a combination of factors. For example, much recent research has focused on methods such as genome-wide association studies, which can identify genetic factors that contribute to disease but do not in themselves yield clinical interventions, although some findings from gene-disease association studies have the potential to serve as biomarkers of risk. Multiple genetic variants have been identified but most confer small relative risks and explain only a small proportion of the heritability for most conditions.[12,13]

One of the most important barriers to the effective translation of clinically relevant research findings is the lack of a comprehensive infrastructure to systematically collect, evaluate, and disseminate evidence of the clinical validity and utility of new tests used for diagnosis, prognosis, screening, and risk assessment based on novel biomarkers including genetic variants. Although some parts of this evaluative process are in place (as manifested by the UK National Institute for Health and Clinical Excellence, the US Food and Drug Administration and US Evaluation of Genomic Applications in Practice and Prevention), the absence of a comprehensive infrastructure raises substantive questions about how such primary data should be generated and collected, and further issues as to who should evaluate and analyze the data, and against which criteria or standards the utility of a test might be measured. Even where existing knowledge is well described and documented, in many cases, it has not been utilized in an effective manner: for example, the continuing failure of many countries to offer cascade testing from an affected individual through their extended families, for known single gene disorders such as familial hypercholesterolemia or inherited colorectal cancer syndromes, continues to allow substantial preventable morbidity and mortality.[14] These deficiencies are exacerbated by limitations placed upon research and clinical capability through prevailing research infrastructures, funding constraints, and competing priorities.

FRAMING RELEVANT RESEARCH

Within the next decade, it seems likely that the focus for medical research funding will be those areas of clinical and public health practice that promise to yield the greatest benefits such as the improved diagnosis and management of single gene disorders, and the application of promising pharmacogenetic tests to improve the safety and efficacy of therapies. Improving our understanding, treatment and prevention of common diseases, such as diabetes or heart disease, will continue to be challenging, because these arise through a complex interaction of genetic and environmental factors during development and over the life course. A number of approaches are needed: novel analytical tools that can accurately and reproducibly characterize and measure both phenotypes and environmental exposures; population biobanks that enable prospective genotype, phenotype, and environmental data to be collected from large cohorts; and effective strategies for integrating all these data for meaningful analyses.[15]

In addition to novel research tools, clinical and population genomic research seems likely to demand innovative (sometimes novel) research methods. Research into rare genetic variants will necessitate larger research collaborations to ensure statistical power and validate findings, with a concomitant need for increased data sharing and transparency. Major technical challenges in the measurement of social and environmental determinants of health, and their interaction with genetic factors, must also be overcome. It is likely that new areas of expertise will be needed that can consolidate medical and bioinformatics knowledge, allowing clinically useful genome annotation to facilitate better medical decision making.

These developments also highlight the immediate need for up-to-date systems and processes for assuring the protection of human research subjects (including professional guidance and ethical codes)[16] while the necessary evidence on the potential benefits from genome-based health care is acquired. For example, the longitudinal collection of gene/environment data from large-scale epidemiological studies may challenge traditional approaches to obtaining informed consent.[17] It may also alter commonly held expectations regarding privacy protection, anonymization, and reidentification,[18] withdrawal from research programs and databases, as well as the feedback of incidental findings[19] and accountability of researchers engaged in the research process. The ongoing debate about the need to ensure privacy while maximizing public good will serve this agenda well.

PRIORITIZING THE TRANSLATION PROCESS

An important reason why genome-based discoveries have not yet realized their clinical and public health potential is that attention and funding have been largely directed at the initial

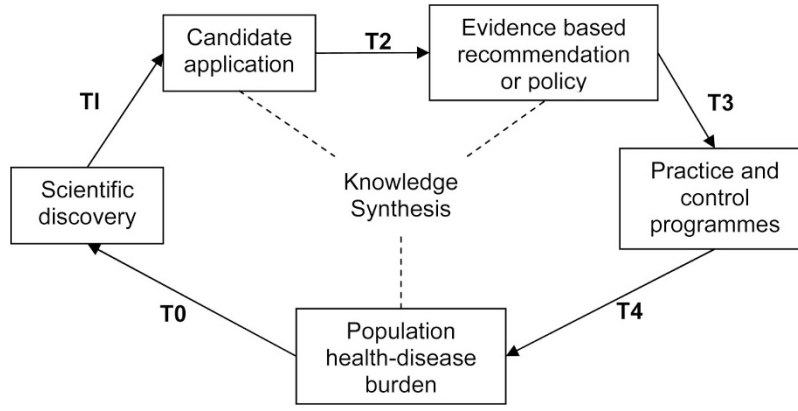

Fig. 1. Knowledge synthesis—the engine of translational research adapted from Khoury et al.[7]

stage of scientific discovery, rather than at the application, implementation, and evaluation stages. The process of transition from genomic research to clinical and public health interventions has been defined as a "translation process" that can be categorized into a cycle of five phases (Fig. 1).[7,20] Although the first phase of translation—of novel drug targets from animal studies to human trials, for example—is managed via the traditional clinical trial framework with acceptable levels of funding, subsequent phases are comparatively under-resourced and lack the necessary infrastructure.[7]

Similarly, although an increasing number of genetic tests are available, their evaluation and subsequent evidence-based implementation into clinical practice is lagging behind. Aside from consideration of resources, the prevailing regulatory environment often dictates the pace of innovation and thereby the speed at which research products is brought to market. Table 1 compares two dysfunctional scenarios, the first in which there are inadequate controls upon releasing new research to the market (Premature Translation) and the second in which the barriers to realizing the benefits of research are so oppressive that new findings are rarely incorporated into better clinical practice (Lost in Translation). Determining the balance between these two extremes will be an important challenge for public health genomics for years to come.

The Ickworth Group strongly supported significant investment in infrastructure for translational research on the grounds that increased investment will build capacity, shape the organization of health systems and services, result in more effective public health programs that incorporate accurate measures of genetic, environmental, and social determinants of health, and provide a powerful means of effectively evaluating new and existing public health interventions.

DELIVERING GENOMICS FOR IMPROVING HEALTH

Although the burden of poverty-related conditions and infections remains substantial in the developing world, the combination of increased affluence, urbanization, and life expectancy has led to a global growth in the incidence of complex diseases, such as cancer, diabetes, heart disease, and poor mental health.[21] There is mounting evidence of diverging health outcomes within and between economically developed countries and both LMIC. Against this backdrop, questions arise about how to prioritize public health interventions and existing clinical services and systems. Frieden[22] has proposed a hierarchical model that prioritizes interventions acting at the population or societal level over more individualistic approaches on the basis that they have the greatest numerical impact at lower unit cost. This has implications for the translation of genomic interventions since most of these act at the level of the subpopulation through to the individual rather than at the whole population.

It was felt that public health professionals should regard biological and social models of disease as complementary and synergistic paradigms in their efforts to improve population health. In deciding between different approaches, a pragmatic approach for policy makers and health services providers might be to consolidate existing knowledge of genetics and inherited disorders and utilize proven approaches such as the use of newborn screening and the systematic use of newborn and disease-specific registries to optimize the use of limited health care resources. At the same time, developments in genomic medicine require a strategic response, which should anticipate an increase in health service requirement, comprising workforce and service development and reconfiguration to meet the increasing need for expertise in bioinformatics and laboratory support.

THE ROLE OF THE PRIVATE SECTOR, COMMERCE, AND INDUSTRY

The private sector has played a pivotal role in the design and development of new genetic technologies, such as lowering the cost of genome profiling and sequencing platforms, which have catalyzed research programs around the world. Consequently, the development and uptake of novel genomic technologies has been heavily influenced by commercial interests, especially since scientific research is increasingly funded through multiple sources.

There was a range of views among workshop participants about the influence of industry upon genomics health research. Some tended to regard industry as having a negative influence to the extent that commercial involvement may influence priorities set for research, the potential for collaboration, publication strategy,[23] and the dissemination of the results of research. Empirical work in this area suggests that potential research participants might be wary of participation if the research is driven by commercial interests, serving to reduce public trust in the research process.[24,25] Others recognized that, despite this public unease, it was important to have mechanisms to support investment in research, such as the patent system, which it was

Table 1 Comparison of two alternative (and dysfunctional) models of translation

Premature translation	Lost in translation
Rapid implementation of novel tests	Promising discoveries are rarely translated into practice
Lack of evidence about clinical validity and/or clinical utility	Requirements for evidence of clinical validity and clinical utility are so onerous that they are rarely satisfied
No information about clinical utility	Valid useful tests where clinical utility is assured
Potential for increased health benefit	Diminished health benefit overall because few tests reach the market
Potentially harmful	Diminished overall potential for harm
Potentially useless tests reach the market	No useless tests reach the market
Use likely to be mediated by experts and public curiosity	Use likely to be mediated by medical professionals
Researchers may be encouraged by their work being made accessible	Researchers may be disenchanted because discoveries rarely reach the public
Many tests are implemented	Few tests are implemented
Lack of professional and public engagement	Lack of professional and public engagement
Commercial engagement if markets grow	Lack of commercial engagement
Increased commercial investment	Dwindling public and private investment
Innovation stimulated	Innovation stifled

Adapted from material presented at the Ickworth meeting by Professor Muin Khoury.

argued provided a "structured equilibrium" for research albeit in the face of recurrent legislative challenges.[26]

Notwithstanding the importance of such measures, there was some agreement that the existing system of patent protection was not well suited to protecting the intellectual property of those seeking to develop biomarkers and diagnostics for use in health care. Moreover, where technologies are characterized by low profit margins, high volumes, and intense competition, the nature of the products tested and the means of testing should not be driven by market forces but by a health improvement agenda through improved clinical practice or public health population screening programs. Population health may best be served initially by publicly funded mechanisms together with efforts to craft public-private partnerships.

Direct-to-consumer genetic testing

A novel development has been the emergence of a small direct-to-consumer market for genetic tests. The principal providers tend to offer a suite of genetic testing ranging from ancestry testing through to predictive disease susceptibility testing that may provide medically actionable results. There is potential for individuals who access predictive testing in this way to be harmed and also concerns about the potentially adverse impact of such testing upon existing health services and systems.[27] However, preliminary evidence suggests that the fledging market remains modest,[28] and evidence from related disciplines (such as clinical psychology) suggests that there is a limited scope for such predictive tests to motivate behavior change,[29,30] and that more traditional public health approaches such as risk reduction, through environmental change or legislation, may be more effective.[31]

Although the Ickworth Group did not reach a consensus regarding the extent of regulation that should apply to direct-to-consumer genetic tests, particularly those with scant evidence of clinical validity or utility, it was agreed that transparency is needed to ensure that both physicians and consumers are able to make an informed choice: evidence of clinical validity and utility should be made available (or its absence flagged) and rigorous ethical standards for obtaining consent and safeguarding consent and confidentiality should be promoted. The most effective means of facilitating consumer protection and education might be at government level.

GLOBAL PUBLIC HEALTH

Public health genomics and LMIC

It is now well recognized that the intersection of global public health and genomic science necessarily implicates ethical issues.[32] Some of these issues reflect past misuses of genetic science in the interest of advancing a national or international eugenic agenda.[33,34] But other issues are more pragmatic insofar as concerns arise about equity in the provision of health services to disadvantaged groups in both economically developed and developing countries.[35] Indeed, Macklin[36] has persuasively argued that one cannot discuss key issues in population health, such as access to essential medicines, without engaging in a discussion about global justice and human rights.

Therefore, one objective of the workshop was to examine the particular relevance of public health genomics to LMIC, given that the stark reality for many populations within these countries is a burden of chronic ill health and disease that is overwhelmingly determined by economic, social, and, sometimes, political factors.[37] A combination of factors such as poorly resourced households, inadequate health care systems, and limited access to health care may provide additional challenges for the implementation of public health genomics. Thus, a major challenge is to generate an evidence base that can demonstrate that a genomics approach is at least as safe, effective, and cost effective in these settings, as other more traditional approaches, such as modifying environmental or social determinants. It is possible that well-designed studies may demonstrate only a limited role

for genome-based interventions for the foreseeable future. Until that evidence is available, however, public health programs and associated clinical services in LMIC are likely to focus upon a few key areas where evidence of clinical utility is well established (such as the antenatal and neonatal detection of certain inherited disorders), or where low-cost solutions are available (such as more systematic use of family history information) or where there is scope for targeted innovative technological solutions (such as the use of genomic-based knowledge and technologies for the diagnosis, prevention, and treatment of infectious diseases that are prevalent in LMIC).

Building research capacity in LMIC

Since most human genomics research has been undertaken in populations of European ancestry, many of the findings (particularly those based on common polymorphisms) are not directly applicable to other populations. This lack of generalizability is compounded through a combination of technological, historical, practical, and circumstantial issues. Existing research tools such as current genotyping chips are primarily based on common variation in Eurasian cohorts, and evidence of gene-disease association in other populations is often absent or incomplete. Moreover, disease prognosis, morbidity and mortality, and the resultant public health responses are likely to be influenced by variations in social and environmental exposures, dietary intake, and a sustained limitation on daily calorie intake coupled with limited access to health care. As a result, research findings from the economically developed world may be difficult to extrapolate to LMIC and vice versa despite their converging demographic profiles. Some efforts are already underway to build research capacity in LMIC especially in the area of science[38] and ethics review of research[39,40] and to undertake genetic research studies involving investigators from LMIC and economically developed countries.[41,42]

The Ickworth Group recognized that in order to address these issues, population-based genomic research should be based upon robust multidisciplinary partnerships between high and LMIC. To safeguard meaningful participation by all partners and build capacity and proficiency in population-based research within LMIC, these should be power sharing, have local control, and offer known benefits within LMIC as well as outcomes-orientated research.[43] The long-term goal of such partnerships is to build capacity and proficiency in population-based research (as well as in science and technology more generally) within LMIC, so that in the future they may conduct and apply such research independently.[44]

RECOMMENDATIONS FOR FUTURE GLOBAL PUBLIC HEALTH PRACTICE

Having firmly established the context for the growth of public health genomics and the prerequisites for its development, a further aim of the meeting was to propose a robust set of recommendations that could guide global public health practice in an era of genome-based medicine. The six recommendations that emerged from Ickworth straddle the breadth of public health genomics from research through implementation. They reflect a consensus position that public health genomics has a key role in improving global human health.

1. *Efforts to integrate genomics into public health research and practice should continue*. The integration of genomic sciences with population sciences, the social sciences, and the humanities should be supported and enhanced to assess the contribution of genomics to population health and to evaluate how this information can best be used to improve the health of populations.
2. *An appropriate research infrastructure for generating an evidence-base for genomic medicine needs to be established and maintained*. An infrastructure for population-based research that can systematically collect and evaluate relevant data to assess the impact of genetic variants (together with behavior, diet, and environment) on population health is urgently required, in the form of both cohort studies and population biobanks in developed and LMIC countries, in addition to intervention studies that show health impact and clinical utility.
3. *Model public health genomics programs and clinical services need to be developed, implemented, and evaluated*. These programs and services should take critical account of the risks and benefits involved in implementing genomic applications, particularly in the short term, and should encompass the following objectives:
   - To *formulate* an independent or "honest broker" evaluation process that can discriminate between those genomic applications which can improve health, from those which are likely to result in potential harm and unnecessary health care expenditure through premature use.
   - To *implement* those applications that have potential to improve health through public health tools and local and international collaborations, including clinical services, policy interventions, and education, thus emphasizing the importance of later stages of the translation process.
   - To *develop* and *apply* tools for evaluating and documenting the health impact of those applications.
4. *International collaboration should be promoted*. These goals will be most effectively fostered through international collaboration via international organizations such as the World Health Organization and international networks such as the Genome-based Research and Population Health International Network (GRaPH-*Int*)[5] as well as engagement with national governments and other multinational and/or nongovernmental organizations.
5. *Appropriate genetic services and genome-based research should be fostered within LMIC*. There is a role for appropriately targeted genetic services, as well as genome-based research in LMIC, and these should be supported while taking careful account of contextual issues including social, environmental, political, and economic factors.
6. *Programs, research, and strategies in public health genomics should be informed by accepted ethical principles and practices*. Developments in public health genomics require that attention is focused on managing multiple ethical issues: methods of obtaining informed consent, engaging the public, protecting human participants, assuring responsible stewardship of resources, managing confidential information, and the commercialization of genetic tests. Where ethically informed practices do not already exist, they should be developed.

CONCLUSIONS

Developments in genomics over the past decade suggest a potential to improve population health that has not yet been realized. The current implementation of genomic knowledge and benefits is both ineffectively and inequitably distributed and realization of its potential has been uneven. The proper context for the development of public health genomics should reflect the tension that arises through balancing the long-term promise of increased scientific discovery, against the hype associated with

interventions that are prematurely presented to health care funders or individual citizens. A number of predominant themes emerge from the discussions at the workshop that set the context for the development of public health genomics, identify some of the necessary requisites to its growth, and suggest future research and clinical priorities.

An urgent challenge for public health genomics is to generate an evidence base to demonstrate when use of genomic information can improve population health outcomes in a safe, effective, and cost-effective manner. Initially, resources should focus upon areas where such evidence already exists, with the aim of maximizing/achieving the potential health gains from investment in this area. Specifically, implementation of evidence-based genomic applications should aim to (1) maximize health benefits and reduce disparities; (2) reduce harms and unnecessary health care expenditures from premature and/or inappropriate use of gene/disease information; (3) provide a means of evaluating public health interventions, and (4) deliberatively foster capacity building, growth, and development by convening and sponsoring population-based research (both through biobanking and the creation of large datasets and cohorts). These themes provide the perspective for the formulation of robust recommendations that should guide future public health practice in an era of genomic and personalized medicine.

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