



The impact of genomics on public health practice

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Abstract

Introduction: Genomic science is developing rapidly, and engagement of public health professionals will be necessary to appraise new technologies and use them effectively.

Sources of data: We use established domains of public health and draw on the literature and expert knowledge to illustrate how genomic technologies give rise to new applications.

Areas of agreement: Genomic technologies are useful in rare inherited disease, including population screening programmes, in health care and for surveillance, diagnosis and treatment of infectious disease.

Areas of controversy: It is less clear when and how genetic susceptibility testing will be used for common chronic disease prevention or protection from environmental hazards.

Growing points: Developments in public health practice will be necessary to ensure rapid and effective implementation of genomic science.

Areas timely for developing research: Public health researchers should address how to accelerate the implementation of genomics for health benefit in developed and developing countries.

Key words: genetics, genomics, screening, health protection, personalized prevention, developing world, public health

In 2013, the UK Government signalled its belief in the power of genomic science to produce major benefits for the population by investing £100 million in a

major project to sequence the genomes of 100 000 NHS patients.¹ The project followed many years of investment in genomic science focused on achieving

gains in both health and wealth for the country. But achieving benefits for health will depend on the ability of clinical and public health communities to ensure that new technologies are used effectively, efficiently, equitably and responsibly for the population as a whole. Such aims for the population lie at the heart of public health practice. In this article, we will show how genomic science has already had an impact on health and is likely to be increasingly important for public health in the 21st century. We will use examples across the various domains of public health and make suggestions for necessary developments in public health practice.

The evolving nature of public health

The practice of public health seeks to understand the causes of disease, to predict and prevent where possible and otherwise to diagnose early and treat effectively so that morbidity, disability and death are minimized. Over the last 150 years, the development of powerful epidemiological tools to look at disease in populations has led to the identification of many causal risk factors for disease and provided the basis for disease prevention and health promotion programmes. In the 19th century, huge improvements in population health were made possible through knowledge and action on environmental factors such as poor housing or unclean water supplies. Last century public health programmes were largely aimed at the major lifestyle factors such as smoking, lack of exercise and poor nutrition that lay behind common chronic diseases; and vaccines were developed to prevent infectious diseases. In the last two decades or so, it has been recognized that knowledge of genomics and the application of new technologies can also contribute to the public health armamentarium through providing molecular insights into disease risk and pathology. Though initially work was mainly focused on genetics, namely the diagnosis and care of patients and families with inherited (or heritable) disorders, wider knowledge of the entire genome has enabled sub-populations at risk to be defined through a range of genomic characteristics or variations as well as by different exposures or lifestyles. Individuals with disease can also be grouped

according to genomic factors associated with particular pathology or likely response to treatment. Similarly, pathogen genomics allows identification of genes responsible for characteristics such as antibiotic resistance or increased virulence, which can aid clinical management. Such new capabilities have increasingly enabled the practice of personalized prevention and health care.²

Genomics and the domains of public health

Public health operates across a number of domains. Advances in genomic sciences have pushed forward the frontiers in each of these, with impacts being experienced currently and expected to accelerate in forthcoming years. The contribution of genomics in each domain was nicely set out by the UK Human Genomics Strategy Group³ as shown in Table 1 with examples. This provides a framework for our further discussion.

Genes as determinants of health

The occurrence and manifestation of all diseases are influenced by both genomic and environmental factors. The extent to which diseases are regarded as 'genetic' (more correctly heritable or inherited diseases) or otherwise depends on which have the predominant influences.

Rare inherited or 'genetic' disorders are often referred to as single gene or Mendelian conditions where an abnormality or mutation in a particular gene leads to disease by altering the production of proteins that are necessary to normal physiological processes (for example, the abnormal haemoglobin structure in sickle cell disease). By contrast, the major chronic diseases that affect populations are complex in origin arising from a multiplicity of aetiologies, which, it is now recognized, include both genetic and environmental factors. A further complexity is introduced by the finding of a number of rare Mendelian subsets of common complex diseases. Individuals with inherited mutations in *BRCA1* and *BRCA2* genes have a higher risk of breast and ovarian cancer, and similar subsets

Table 1 Example of the impact of genomics across UK public health domains

Domain	Potential impact of genomics	Examples
Wider determinants of ill-health	Understanding of gene–environment interaction would give insights into disease risk	Sensitivity to radiation-induced cancer is in part genetically determined. ⁴
Health improvement and healthy lifestyles	More intensive lifestyle interventions may be focused on those with increased genomic risk, increasing cost-effectiveness	Current research looks at the use of genetic information to motivate lifestyle modification in those at higher risk.
Prevention of ill-health	Genetic screening programmes to identify those with, or at, risk of severe inherited disorders for themselves or for their offspring	UK linked antenatal and newborn sickle cell and thalassaemia screening programme.
Health-care public health	Genomics will increasingly inform personalized treatment and secondary prevention interventions applied by health-care practitioners	Stratified treatment in cancer; cascade testing for familial hypercholesterolaemia; preventive mastectomy in women with <i>BRCA1/2</i> mutations.
Health protection	Sequencing of pathogen genomes gives opportunities for improved disease surveillance, investigation and control of infectious diseases, understanding host–pathogen interactions	The ability to define genetic markers that predict drug resistance in <i>Mycobacterium tuberculosis</i> has increased especially with the use of whole-genome sequencing. This would allow rapid initiation of appropriate treatment.

exist in colorectal cancer, cardiovascular disease and diabetes.

Because of its interests in disease prevention, and the diagnosis and treatment of disease within health-care systems, public health needs to concern itself with all these categories of disease. For single gene disorders, the main public health priorities are around genetic screening and the effective use of genetic testing within health-care systems to determine best treatment and provide preventive care for at-risk family members. For complex disorders, the main hopes are to be able to predict and prevent disease through identification of those at higher risk. For health protection, applications arise in both the public health and health-care systems.

Genomics and disease prevention through screening

Knowledge and technologies based on genomic science have brought about new opportunities for disease prevention through screening. Notably, genetic testing has enabled major developments in the stages of disease at which screening may be offered. Genetic carrier testing now provides the means of identifying couples at risk of having offspring with serious medical conditions such as sickle cell disease at the preconception

stage by identifying those where both partners are carriers of recessive variants; antenatal genetic testing can identify affected foetuses for conditions such as Down syndrome. Screening of newborns via the ‘heel prick’ test can identify babies who are at risk of life-limiting diseases such as phenylketonuria (PKU), most of which are heritable in origin. Antenatal and newborn screening are firmly embedded in national screening programmes in the UK. However, the opportunities for carrier screening mainly present for ethnic minority populations such as those of Ashkenazi Jewish origin who are at higher risk of rare genetic disorders such as Tay Sachs disease,⁵ or for populations with high levels of consanguinity such as the Pakistani communities who are at higher risk for a range of autosomal recessive disorders.⁶ Systematic population approaches to carrier screening, such as the programme in New York for disorders which are common in Jewish communities,⁷ have been highly successful in reducing disease in these populations.

The potential of screening for genetic changes that might be predictive of late-onset disorders is periodically discussed in scientific and clinical circles.⁸ Important examples include mutations in the *BRCA1* and *BRCA2* genes that account for ~5% of breast cancer and 15% of ovarian cancer cases^{9,10} or inherited

forms of cardiovascular disease such as the lipid disorder, familial hypercholesterolaemia (FH), estimated to affect some 120 000 individuals in the UK.¹¹ It is advocated that the burden of disease could be reduced through the early identification of affected individuals using genetic panel testing and the subsequent use of targeted intervention measures (for example, regular screening, preventive measures such as surgery or drug treatments such as statins) in high-risk groups. At present, genetic screening for this group of conditions is only recommended in certain circumstances (for example, cascade testing from known cases (Lynch syndrome and FH) or testing for women at high risk, because of their family history).¹² Caution is urged before expanding use of such tests to people at 'population-level' risk, because the positive predictive value of any variants found would be much lower, and they would be harder to interpret.

The development of genetic screening programmes at all these life stages in the UK at least is constrained by application of strict screening criteria designed to ensure optimum health benefit with least harm for the population as a whole. For example, only two inherited metabolic conditions (PKU and medium-chain acyl-coenzyme A dehydrogenase deficiency) are screened for in newborns in the UK, whereas around the world >50 conditions are identified as being detectable through the new method of tandem mass spectrometry. After much debate and a 2-year pilot programme, a further four conditions will be added in England from November 2014. However, further pressure to expand programmes will undoubtedly arise as a result of such powerful new genomic technologies that enable faster, cheaper and

safer examination of the genome and the possibility of looking for many conditions at once (Table 2). Public health professionals will have an important role to play in this decision-making but, to do so they will need sufficient understanding of these new genomic technologies, the underlying science and the relationship of molecular pathologies to the diseases are in question. This must be complemented by skills in epidemiology, evidence and cost-effectiveness; their wider awareness of social implications such as stigmatization and the likely effects of new screening programmes on the organization of health services.

Genomics and health care

It is perhaps in the field of health care that genomic science will have its most profound effect, particularly in the short- to medium-term. By providing powerful new tools to diagnose disease at a basic molecular level, it can be used to streamline diagnostic pathways and enhance clinical decision-making. In recent years, it has come to be regarded as one of the most powerful technologies enabling the current drive towards personalized medicine.¹⁵

Rare disorders of which at least 80% have a genetic origin contribute significantly to the clinical caseload in all specialties, particularly paediatrics. The burden of morbidity they impose on the younger population is increased, because such diseases often have onset in childhood and are lifelong affecting many body systems. One of the major problems in effective and efficient management of people with rare disease is the time it takes to get a diagnosis. This typically takes several years and involves referrals to

Table 2 New technologies giving potential for expansion of screening

New technology	Possible demand on screening programmes
Antenatal testing using cell-free foetal DNA obtainable from a maternal blood sample without risk to the foetus ¹³	Demand for screening of a wider range of conditions, including single-gene disorders, chromosomal disorders such as Down's syndrome and even late-onset disorders
New sequencing techniques that enable genome-wide examination (currently undertaken for diagnostic purposes)	Calls for opportunistic testing for serious conditions that may be amenable to prevention ¹²
Tandem mass spectrometry	Recommendation in the USA to screen for 31 core conditions ¹⁴

many different clinicians and a multitude of investigative tests. Such protracted processes use health services resources to no avail while the condition often deteriorates without appropriate management. However, as genetic tests become more powerful, quicker and cheaper, the use of genetic testing earlier in a diagnostic pathway is increasingly advocated. For example, genomics 'array' testing as a first-line test for the paediatrician investigating developmental delay has been shown to be cost-effective compared with current pathways.¹⁶

Diagnosing a serious inherited disease may give family members the opportunity for reproductive choice. This may be very important for parents who have had an affected child. Identification of the precise mutation involved in that child's disease enables the foetus, or even an embryo in the pre-implantation stage, to be tested so that the parents can take decisions not to allow a pregnancy to continue (or be established) if the child will be affected.

Of equal importance are the opportunities to identify family members who might be at risk so that they can be offered preventive treatment at an early stage. Returning to the example given above of FH, which leads to accelerated development of atherosclerosis and premature coronary heart disease with 50% of men and 30% of women being affected by age 55,¹⁷ it is estimated that in the UK only ~15% of the 120 000 affected individuals are identified and receiving treatment. In 2013, a UK-focused workshop noted that new public health structures provided an opportunity to deliver systematic 'cascade' testing for FH that would start by discovering relevant mutations in affected individuals and sequentially test family members. They described such a programme as a 'quick win' for reducing cardiovascular disability and death in young people and one that would ultimately save health service expenditure. However, they emphasize that an integrated approach covering the whole disease pathway and involving many organizational players including public health would be required.¹¹

Genetic testing may also be used to identify important single gene subsets of disease that require different treatments. Diabetes provides a good example where identifying the genetic subtype Maturity Onset Diabetes of the Young (MODY) indicates to the

physician that the patient will respond well to drug treatment with sulphonylureas rather than requiring insulin.¹⁸

Cancer patients are cared for across all specialties within the health-care service and are a major user of health care with over 330 000 new cases in the UK each year.¹⁹ Again, genomics is transforming care in this area. The detection of a tumour's genetic signature may be used to make a precise diagnosis, enabling a more accurate prognosis and better-tailored treatment. Increasingly, drugs are available that are targeted to the genetic features of a cancer, requiring genetic testing of the cancer cells to determine their potential response. For example, chemotherapy drugs such as *Cetuximab*, used for treating metastatic bowel cancer, target the epidermal growth factors (EGFR) signalling pathway to inhibit tumour growth. Their efficacy relies on the tumour cells retaining a normal KRAS protein; those tumour cells that have a mutated overactive KRAS will be resistant to anti EGFR therapy.²⁰

In the UK, a Government White Paper in 2003 and a more recent strategic report on genomics presented to the UK Department of Health and other government offices²¹ have identified that developments in clinical applications of genomics are taking place throughout clinical medicine and not just within the confines of specialist genetic services. Alongside the development of laboratory services for accurate analysis and clear reporting that supports decision-making, both documents stressed that clinicians in all mainstream specialties will need to integrate these new 'genomically enabled' pathways for diagnosis and become competent at ordering and interpreting tests for their patients. What is perhaps less widely acknowledged is that these new paradigms will need to be shaped and developed on a population basis through public health advice. The importance for health care public health lies in ensuring that innovation is evidence based, cost-effective, timely and equitable.

Genomics and common chronic disease prevention

Cardiovascular disease, cancers, diabetes and mental health disorders are the common chronic diseases

that form the main focus of attention for public health programmes in the developed world. The traditional focus of public health attention is based not only on the importance of burden of disease arising from these conditions, but also on the characteristic perception that they are amenable to prevention given knowledge about the importance of external risk factors such as smoking, diet or physical activity.

For most of these conditions, recent scientific research in the form of genome-wide association studies has identified susceptibility variants that contribute to the distribution of disease in populations. Characteristically, modelling shows that the risk of disease is double the population average in the 5% of the population at highest risk. This leads to the possibility for preventive public health that genetic testing could enable the population to be stratified by risk and preventive interventions targeted accordingly. For example, stratification of breast cancer risk may enable mammography to be offered earlier or more frequently to those at higher risk and less frequently, at a later age, or not at all to those at lower risk. Such strategies offering more intensive primary or secondary prevention interventions to those at greater genomic risk will become increasingly important in public health programmes that seek to maximize benefit while minimizing inconvenience or even harm and providing cost-effective services.²²

Health protection

Despite a general decline in infections globally over the century, infectious pathogens remain important causes of morbidity and mortality with new and emerging pathogens continuing to pose a threat to global public health. The use of molecular and genomic approaches to study infectious disease aetiology, pathogenesis, prevention and treatment has recently substantially increased.²³ New sequencing technologies applied to pathogen genomes have multiple uses in the area of infectious disease, including surveillance, investigating transmission and understanding pathogenesis. Relatively cheap sequencing of pathogen genomes allows rapid characterization of microorganisms, identification of key virulence factors and antibiotic resistance profile (useful in determining

the best treatment options for a given patient), monitoring the spread of antibiotic resistant strains and detection, mapping and analysis of outbreaks. It has already been used to identify the probable sources of both hospital- and community-based disease outbreaks.

Within surveillance, whole-genome sequencing allows trends (for example, in drug resistance or vaccine escape) to be identified and monitored in more detail than is possible with conventional surveillance methods; this in turn allows the development of hypotheses that can be rigorously tested in epidemiological studies. For example, based on a phylogenetic tree constructed using whole-genome sequences from clinical isolates of methicillin resistant *Staphylococcus aureus* (MRSA), Harris *et al.*²⁴ identified instances of probable international spread and also estimated that the responsible MRSA clonal lineage (ST239) emerged in the mid-to-late 1960s, a date which was consistent with the timing of increased antibiotic usage and the first detection of MRSA in Europe. Vaccine escape mutants have been identified through phylogenetic analysis of isolates of the PMEN1 clone of *Streptococcus pneumoniae*; recent (2005–07) isolates from the USA were distinct from older USA isolates, implying that the introduction of the heptavalent pneumococcal conjugate vaccine in 2000 had changed the population distribution of the organism.²⁵ Genome sequencing can also provide baseline data before the introduction of a vaccination programme, allowing prospective evaluation of potential changes in epidemiology.²⁶

Whole-genome sequencing can supplement traditional epidemiological methods in studies investigating transmission of infection. It has potential uses in investigating both small clusters and larger outbreaks of infection, providing timely information on evolutionary origin, route of transmission, pathogenic potential and drug resistance (if genes and/or gene variants influencing these characteristics are known). Comparing the genome sequences of pathogens isolated from different hosts can aid in inferring patterns of transmission when considered together with epidemiological data. Although the identification of two identical strains cannot prove that two cases are epidemiologically linked, putative chains of

transmission can be ruled out if the infecting strains are found to be different. Genome sequencing has been used in a variety of outbreak investigations to establish likely networks of transmission and explain the mechanism of spread through a population, e.g. transmission of MRSA within and between hospital units and the community,²⁷ persistence of *Klebsiella pneumoniae* on a ventilator despite thorough cleaning²⁸ and identifying potential superspreaders.²⁹ It has also been used to identify likely camel-to-human transmission of the Middle Eastern Respiratory Syndrome coronavirus.³⁰ For animal health, WGS of pathogens isolated from different animal hosts can help to elucidate the transmission dynamics within and between species, e.g. the transmission of *Mycobacterium bovis* between cattle and between badgers and cattle.³¹

Genome sequencing can improve understanding of the natural history of infection, for example inferring whether a second episode of tuberculosis disease in a particular patient is due to relapse or reinfection.³² Whole-genome sequencing can also be used to identify virulence factors, which in the future may be investigated for associations with pathogenicity, mortality, transmissibility and drug resistance.³³ It can also provide insights into the likely processes through which drug resistance develops. For example, the structure of the phylogenetic tree in relation to drug resistance, constructed for *M. tuberculosis* strains isolated in Russia, suggested that resistance to fluoroquinolones and pyrazinamide was acquired during infection rather than pre-existing in the infecting strain; this in turn suggested that strains resistant to these antibiotics might be less transmissible than susceptible strains.³⁴

While there is much potential for genome sequencing to become a useful tool for infectious disease epidemiologists, it does have potential limitations. Studies involving whole-genome sequencing are subject to the same potential sources of error as any epidemiological study (such as chance, bias and confounding). Additional considerations for genomic epidemiology studies include the need to distinguish between asymptomatic carriers and symptomatic patients, the standardization of laboratory methods and the ease with which particular loci of interest

can be sequenced (e.g. sequencing repeat regions is problematic). The definition of strain differences, e.g. in terms of numbers of single-nucleotide polymorphism (SNP) differences (variation in a single base pair of DNA), can also be difficult. Although the costs of genome sequencing are rapidly declining,³⁵ the cost-effectiveness of use in routine practice needs to be evaluated.

The developing world perspective

We have focused so far on what genomics may achieve for traditional public health domains within the context of the UK or other westernized or developed countries. But genomics can provide tools for worldwide health, and the concerns of the public health community should go beyond the constraints of national boundaries. As well as the health divide that exists between rich and poor countries, during the last 10 years a large gap has also been exposed in the capacity of countries to carry out biomedical research. This means that increasingly high-income countries define the agenda for research; results are most relevant to them, and an accelerating health divide becomes inevitable.³⁶ The 2002 WHO report 'Genomics and World Health' identified many concerns and opportunities for using genomics to improve world health, many of which remain largely relevant today.³⁷

As described by Kumar³⁸ in a major textbook on genomics in the developing world, for many developing countries the main opportunities remain those around inherited disorders. For example, sickle cell and thalassaemia, with their recessive inheritance patterns, cause major burden of disease, especially in countries where there are high levels of consanguinity. The burden of disease in developing countries from preventable birth defects prompted the World Health Assembly in 2010 to declare this as a significant problem and urged them to take action. However, many barriers to such action exist, including difficulties in persuading senior policymakers to recognize the potential of genomics, and the lack of genetic expertise and service provision available for these very large, poor populations. One tool that enables policymakers to make a rapid assessment of

Table 3 Resources for further education in genomics for public health

Office of Public Health Genomics, Western Australia, leads on the translation of genomics knowledge into health benefits framed around evidence-based policy for genetic services, implementation of genetics and technologies and screening policy.

<http://www.genomics.health.wa.gov.au/publications/>

The Office of Public Health Genomics (OPHG), CDC, takes a lead role in the USA in identifying, evaluating, and implementing evidence-based genomics practices to prevent and control the country's leading chronic, infectious, environmental, and occupational diseases.

<http://www.cdc.gov/genomics/public/index.htm>

The PHG Foundation in Cambridge, UK, an independent organization focused on translation of genomic technologies for improved population health.

<http://www.phgfoundation.org/resources>

CDC Centers for Disease Control and Infection describes public health application of pathogen genomics.

<http://www.cdc.gov/genomics/pathogen/>

need in their own country and develop policy options around birth defects was developed by an international group led by the PHG Foundation in Cambridge.³⁹ For pathogens, it is unlikely that whole-genome sequencing would play a major role in routine clinical practice in the developing world but molecular testing technologies such as Xpert,⁴⁰ which detects genetic variants that confer rifampicin resistance in *M tuberculosis*, are now widely used in some developing countries.

Increasing amounts of biomedical research are now being carried out in developing countries. However, it seems fairly certain that an international programme will be required to assist countries in developing their infrastructure and capacity for genomics in both research and health care. For the former, it will be vital that all countries are enabled to contribute data to, and learn from, major international collaborations such as the recently launched Global Alliance for Genomics and Health (<http://genomicsandhealth.org/>), which is focused on ensuring effective and responsible sharing of clinical and genomic data around the world. For the latter, it seems clear that lower and middle income countries should stand on the shoulders of developed nations, creating health services that embrace the most recent technologies and practices. In the field of pathogens, it is highly likely that knowledge gained from genome-wide association studies and pathogen genome sequencing will lead to the development of new diagnostics and treatments,

including new antibiotics and antibacterials that would eventually be available in the developing world.

Conclusions

In conclusion, new genomic knowledge and technologies offer exciting opportunities for more effective disease prevention, protection, diagnosis and care across all the domains of public health practice. Although this may seem at present to remain largely confined to research and specialist practice, this is changing rapidly.

We have discussed the need for public health professionals to become knowledgeable about genes as determinants of health, about how genomic testing will be used in screening, disease prevention and health care and particularly noted its potential in the control and treatment of infectious disease. We have noted some of the technical skills that will be required along with some of the wider ethical, legal or social issues that also need to be considered. Although we have used the UK framework for discussion, Table 3 provides links to worldwide public health genomic organizations that provide educational resources and up-to-date news in this rapidly moving field.

With their unique perspective on outcomes for the population as a whole and their multidisciplinary skills, we have illustrated how public health professionals can potentially play a major role in shaping

these developments. However, they will need to acquire the necessary knowledge and understanding to properly integrate this into their practice.

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Conflict of Interest statement

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