

VIEWPOINT

Personalized genomic information: preparing for the future of genetic medicine

Alan E. Guttmacher, Amy L. McGuire, Bruce Ponder and Kári Stefánsson

Abstract | The falling cost of sequencing means that we are rapidly approaching an era in which access to personalized genomic information is likely to be widespread. Here, four experts with different insights into the field of genomic medicine answer questions about the prospects for using this type of information. Their responses highlight the diverse range of issues that must be addressed — ranging from scientific to ethical and logistical — to ensure that the potential benefits of personal genomic information outweigh the costs to both individuals and societies.

Q *Are we already at a stage at which we need to consider how personalized genomic information can be used?*

Alan E. Guttmacher. Personalized genetic information (that is, information about a limited number of specific genes) has long been part of many individuals' health care and health records. The most pervasive use of such information has long been newborn screening. Indeed, for decades the vast majority of newborns in many countries have undergone screening that tests for various conditions caused by mutations in specific genes¹.

By contrast, we have not yet entered the era in which personalized genomic information (that is, information about much or all of a person's entire genome) is a common part of health care or health records. However, that era will be soon upon us² and, unless we prepare now, we will not have the scientific, logistical and ethical framework that is required for the appropriate and effective use of genomic information. And, unlike past uses of genetic information, future uses will include issues that are well outside of what most would recognize as health-care applications, ranging from forensics to prediction of behaviour to

potential eugenics. Clearly, this wide range of uses broadens the issues that we need to address.

Amy L. McGuire. Absolutely. Technological advances over the past decade have made it possible to generate whole genome sequences at a relatively low cost, and many predict that the US\$1000 genome is just around the corner³. In addition, companies are offering extensive genotype information directly to consumers. Admittedly, the ability to generate personal genomic information has outpaced our understanding of its functional significance, limiting its present clinical utility. This presents the perfect opportunity for the medical and scientific communities to adopt a preventive approach and to consider the appropriate and inappropriate uses of personal genomic information, both now and in the future. For example, premature clinical integration of genomic information may lead to a cascade effect⁴, resulting in inappropriate follow-ups that are potentially harmful and that would constitute an unjustified use of health-care resources⁵. Conversely, the appropriate integration of pharmacogenomic test results may save lives and lead to improved patient care⁶. As research advances, what constitutes an appropriate use of genomic

information will change. Studying how stakeholders are using and plan to use this information can help to shape public policy and inform professional guidelines.

Bruce Ponder. Yes. Tests are already being marketed, but there are many issues to be addressed. The first is how to demonstrate benefit. The applications of genomic information in medicine will be mostly to provide information about the balance between costs and benefits in decisions about screening, prevention and need for treatment⁷. We need to consider carefully how to recognize the situations in which the additional information from genome testing might be of most help either to individuals or in the context of public health, how to estimate the likely costs and benefits, how to design and conduct the studies (which may involve thousands of subjects followed for many years) to demonstrate that the proposed medical benefits are true and, finally, how to factor in the economic, social and ethical terms to the equation.

We must also consider questions of education and understanding. The medical decisions for which genomic information will be used are often complex and involve probabilities, not certainties. How should we equip individuals to think about risks of disease balanced against risks of intervention? In particular, if tests are to be sold directly to consumers, measures will be needed to ensure that individuals receive appropriate information and advice. Genomic testing will highlight issues of access to medical interventions based on risk, which will raise potentially difficult issues of equity and acceptance.

Finally, when do 'medical' genomics-based predictions shade into predictors of more general personal attributes — such as personality and longevity — and how will we respond to the implications of these issues?

Kári Stefánsson. There is still no consensus on whether recent discoveries about the genetics of common diseases have brought us to a stage at which we need to begin to consider how personalized genomic information should be used to benefit individuals and, through that, society in general. There are those who insist that the risks conferred are too small to be of any use⁸.

The contributors*

Alan E. Guttmacher is the Acting Director of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development at the US National Institutes of Health (NIH), Bethesda, USA. Until 1 December 2009 he was the Acting Director of the National Human Genome Research Institute (NHGRI) at the US NIH. In that role, he oversaw the NHGRI's efforts to advance genome research, integrate that research into health care and explore the ethical, legal and social implications of human genomics. A paediatrician and medical geneticist, he also previously served as the NHGRI Deputy Director and as Director of its Office of Policy, Communications and Education.

Amy L. McGuire is an assistant professor of medicine and medical ethics and an associate director of research at the Center for Medical Ethics and Health Policy, Baylor College of Medicine, Houston, USA. Her research focuses on legal and ethical issues in genetics and genomics, with a particular focus on genetic research and personalized genomic medicine. She is currently studying participant attitudes towards broad data sharing in genome-wide association studies, ethical issues in human microbiome research, and consumer expectations regarding the clinical integration of direct-to-consumer personal genome testing services.

Bruce Ponder is Li Ka Shing Professor of Oncology at Cambridge University, UK, and Director of the new Cancer Research UK Cambridge Research Institute. His research interests are in genetic predisposition to cancer. In 2007, with colleagues in Cambridge, he published the first genome-wide association study for breast cancer, and the Cambridge group have recently participated in a similar study in ovarian cancer. As a clinician, and founder of one of the first familial cancer clinics in the UK, he is interested in the practical application of the results from genetic studies.

Kári Stefánsson has served as president, chief executive officer and a director since he founded deCODE genetics in August 1996. He was appointed chairman of the board of directors of deCODE genetics in December 1999. From 1993 until April 1997, he was a professor of neurology, neuropathology and neuroscience at Harvard University, Cambridge, USA. From 1983 to 1993, he held faculty positions in neurology, neuropathology and neurosciences at the University of Chicago, USA. He received his M.D. and Ph.D. from the University of Iceland, Reykjavik, and is board-certified in neurology and neuropathology in the United States. The goal of his research is to understand how diversity in the human genome sequence leads to human diversity. He has published numerous articles on the genetics of common and complex traits and has discovered variants in the sequence of the human genome that are associated with heart attack, type 2 diabetes, prostate cancer, schizophrenia, glaucoma, atrial fibrillation, nicotine dependence, recombination rate, thyroid cancer, urinary bladder cancer, melanoma, obesity and breast cancer.

*Listed in alphabetical order.

It is true that the effect of each sequence variant may be modest or small. In many common diseases, however, several associated variants have been discovered and their combined effect is formidable and may be of considerable clinical value. It is important to keep in mind that if the disease is very common, the relative risk does not have to be large to be clinically relevant. The example I would like to use is that of heart attack. If we take 12 recently discovered sequence variants that are associated with the risk of heart attack and that are independent of known risk factors⁹⁻¹⁴, they can be used together in a genetic test for the risk of heart attack. This test alone can allow for the identification of the 10% of people of European descent whose risk of developing a heart attack is 1.6 times greater than the population average. As the lifetime risk of suffering a heart attack is 49% for men over the age of 40, this test allows us to find men who have on average a 79% lifetime risk. Individuals who are in the top quintile of the concentration

of low-density lipoprotein cholesterol have a heart attack risk that is 1.3 times the population average, which translates into a lifetime risk of 64%. Hence, a genetic test based on recently discovered sequence variants could identify people with an added risk of heart attack that is twice that of those who are at the top of the cholesterol curve. In this context, it is important to keep in mind that the ability to assess the risk of heart attack by measuring serum cholesterol has transformed cardiology into the most important field of preventive medicine.

As an example of a situation in which a new genetic test based on common variants would not be useful, consider a test for the risk of multiple sclerosis that would allow us to identify 10% of the population with 1.6 times the population average risk of developing the disease. The population risk of developing multiple sclerosis is only 0.1%, which for the individual is not markedly less than the risk of those who are positive for the test (0.16%).

Q Is direct-to-consumer genetic profiling helpful?

A.E.G. There is a long tradition of underestimating the ability of patients to understand information about their health. Well into the twentieth century, most physicians thought it inappropriate to write articles or books about pregnancy aimed at the lay public. Today, bookstores have large sections devoted solely to such works, and mothers and newborns seem not only to have survived this democratization intact but also to be better off for their empowerment.

To state the obvious, information is power, and particularly so when it is about yourself. A process that enables individuals to learn about themselves has the potential to be truly empowering. However, if the process is not fact-based or does not supply a context that allows the individual to understand and harness the information, it can lead to misinformation, misunderstanding, misjudgement or misbehaviour. The challenge for direct-to-consumer genetic profiling is much like the challenge for any direct-to-consumer information; it must be accurate and understandable, and its implications and limitations clear. If direct-to-consumer genetic profiling develops such that consumers gain power over their health and lives, it should be largely helpful. If it develops, instead, such that purveyors simply gain power over consumers, it will be largely harmful.

A.L.M. Much of the information that is provided by direct-to-consumer companies is recreational (for example, ancestry information and information about traits such as bitter taste and running speed). This information may not be helpful in the clinical sense, but it is likely to be harmless, and consumers may find it interesting or entertaining. Most direct-to-consumer companies claim that all of the information they provide is recreational (see, for example, [23andMe](#)), but the US Government Accounting Office has found that some of this information is health-related and could be interpreted as diagnostic¹⁵. For this type of health-related information to be helpful clinically, it must be valid and have proven clinical significance. Direct-to-consumer profiles that report genetic associations with odds ratios of 1–2 arguably lack clinical utility. Knowledge of this information would only be helpful if it leads to improved health behaviours, which are recommended regardless of one's genetic profile. For more highly penetrant genetic variants, professional

judgement is required to assess the significance for the individual and to determine appropriate follow-ups in the context of a complete medical evaluation¹⁶. Therefore, direct-to-consumer genetic profiling that is provided without the involvement of a competent health care provider may not only be unhelpful, it may be harmful.

B.P. Is checking your own blood pressure or cholesterol helpful? With any test, it depends upon the action that follows and whether it is appropriate. There has been an idea that somehow genetic information is different and more dangerous than other types of medical information. This voodoo idea should not colour the debate: genomic information should be evaluated and used in the same way as any other medical test. Even the implications for other family members are not generally different from those of an observable family history or a diagnosis of diabetes or hypertension.

The possible advantage of direct-to-consumer testing is that it will be quicker and cheaper than the traditional face-to-face consultation, so more information can reach more people. And there is the principle that if people want information, they should be able to get it. However, information is like a pill — once swallowed, it is impossible to retrieve. So, just as with pills, there is a duty of government and society to ensure that the pill is accurately labelled and is used appropriately.

Given the complexity of the medical questions that testing may raise, one must ask whether written information alone can ever be adequate. Medical consultation and possible further investigation might be offered through the testing company, but this raises the possibilities of conflicts of interest and inappropriate intervention. Alternatively, in a socialized system the availability of commercial direct-to-consumer testing may carry the risk that the rest of us will pick up the health-services bill for increased demand, again not all of which may be appropriate. I would like to see all direct-to-consumer testing, as well as testing offered through the health services, within a framework of regulation and rigorous evaluation of its effects.

K.S. Over the past decade or so there has been a substantial change in the behaviour of consumers of health care. Today there is hardly a patient between the age of 15 and 70 who goes to see a physician for a new condition without having downloaded from the internet a large amount of information on their condition. It could be argued that

thereby the consumers of health care are taking more control of their own affairs. Access to information about the genetic risk of diseases would allow this development to proceed to the next level. The man who knows the nature of his disease is more likely to seek appropriate help to treat it, and by the same logic a man who knows the risk he has of developing a disease is more likely to seek help to mitigate the risk. It is also important to recognize that by learning about your genetic risk of diseases, you are simply learning about certain aspects of who you are. One of the assumptions of our culture is that it is always helpful to learn in more detail who you are. It is important that people can access this information without having to go through a health-care professional because such an intermediary could serve as a barrier. There is no evidence in support of the notion that knowing your genetic risk of common diseases is harmful.

Q *What will be the longer-term impact of personal genomic information?*

A.E.G. Genomic information has already begun to alter understanding of human biology, health and disease, as overtly demonstrated by the spate of genome-wide association (GWA) studies of the past four years (see the National Human Genome Research Institute [Catalog of Published Genome-Wide Association Studies](#)). Many see GWA studies as primarily providing personalized genomic information about risk for disease. Although GWA studies certainly do that, what they say about the underlying biology of disease is perhaps even more important. The first disease for which a GWA study was performed, age-related macular degeneration (AMD), is but the first example of this¹⁷. A series of GWA studies implicated several genes involved in inflammation in the pathogenesis of AMD¹⁸. Before these studies, few thought inflammation was an important part of the causation of AMD; now, new approaches to treatment and even prevention of the disease are possible.

GWA studies and other sources of personalized genomic information will have other important long-term impacts. They will enable health care based on individual biology (and, eventually, individual environmental exposure information), rather than our current 'one size fits all' paradigm. We will no longer treat patients as representatives of large categories of humanity, but as the individuals that they truly are. This will be among the most transformative changes in the history of health care.

A.L.M. It is hard to know what the longer-term impact of personal genomic information will be. Some believe it will transform the practice of medicine and empower consumers/patients to take personal responsibility for their health and become active participants in their medical care¹⁹. Others worry about the 'Gattaca effect' and fear that the routine generation of personal genomic information will lead to social stigmatization and marginalization and an overwhelming demand for genetically superior 'designer babies'²⁰. Both of these predictions are grounded in hype and a deterministic view of genetics. More realistically, personal genomic information will become one, among many, clinical factors that are considered in medical diagnostics and treatment planning. Medicine has always been 'personal', and good medicine requires a comprehensive approach to clinical care. The ability to generate whole-genome sequences represents a major technological advance. However, contrary to early predictions, we are already beginning to see that the clinical integration of such information will affect the practice of medicine gradually and in subtle and nuanced ways.

B.P. Personalized genomic information will alter the way we think about screening and prevention. Although risk criteria — most obviously age — are used in current programmes, they are still generally thought of as whole-population interventions. Now, just as with individually tailored treatment for disease, we are starting to think in terms of targeted interventions for specific groups. The design and evaluation of programmes for screening and prevention will change.

Better definition of disease subtypes will allow treatment to be matched to the individual, including the more effective evaluation and development of new drugs, with a reduced risk of discarding new treatments that are effective in a specific small subset of patients. For variants that carry a significant attributable risk, mechanism-based prevention might conceivably lead to a substantial reduction in disease burden. In cancer, germline genetic variation may influence somatic pathways or host responses to tumour development; if so, it might prove an additional prognostic in decisions over the aggressive management of screen-detected lesions. Ultimately, early-life profiling for risks of a spectrum of diseases might be the basis for individually tailored lifelong programmes of risk reduction. However, we need much more information before we can judge how much of this potential can be realized.

K.S. Personalized genomic information is going to drive the paradigm shift from interventional to preventive medicine. This paradigm shift is the only way in which health-care costs are going to be contained in a meaningful manner.

Q *How do you see this information being used most effectively?*

A.E.G. Eventually, personalized genomic information will become a cornerstone of everyday health care. By personalizing disease risk calculations, it will improve preventive medicine approaches by personalizing them; for instance, suggesting chemoprevention for men with greatly increased risk for prostate cancer²¹. By making certain causes for a symptom constellation more likely in a given individual, it will guide many diagnostic work-ups. It will improve therapeutics by making it possible to sometimes subcategorize an individual's disease process according to its underlying biology. It will improve pharmacological efficacy by allowing drug selection based on the patient's individual genome and therefore drug metabolism profile²².

Perhaps population-based public health screening is the least obvious area of health care for personalized genomic information to have an impact on, but even here its effects should be felt. As valuable as population-based screening programs are, they are currently blunt tools, and personalized genomic information will individualize and therefore sharpen them. For instance, using knowledge of genetic make-up to individualize recommendations for when to start and how often to repeat mammography or colonoscopy might improve both health care and health economics. And using personalized genomic information to calculate a pre-test likelihood of harbouring prostate cancer might even improve the predictive value of prostate-specific antigen screening²³.

A.L.M. More than 100,000 people die each year from adverse drug reactions²⁴. Pharmacogenomics holds great promise for helping to reduce this number, but it will never be an exact science. Again, genetics is just one factor to consider when treating patients or determining drug dose. This information will be used most effectively when it is combined with other clinical and environmental information to develop a comprehensive view of a patient's history, current medical condition and future risk. The integration of personal genomic

information with other clinical information in a dynamic electronic health record (EHR) will maximize the utility of this information, but it will require advanced informatics and a major international investment to create a common vocabulary that can be used to make EHR systems interoperable and to develop clinical practice guidelines with the interpretive algorithms that are necessary for the facilitation of effective genomic counselling²⁵.

B.P. Classification of the population into high and low risk groups to target interventions such as screening and prevention will be important, provided that enough of the variation is scoreable to provide useful discrimination⁷. But before then, any clear correlation between genotype and risk that affects a medical choice can potentially lead to effective applications: for example, testing for highly penetrant mutations, such as for breast cancer susceptibility (*BRCA1*), predicting the toxicity of drugs or radiation, and genetically classifying disease subtypes that require different management. The higher the odds ratio associated with the genotype, the more effective the application will be. The advent of genome-wide resequencing for searching for rare variants with odds ratios of 2 to 4 will be important²⁶.

We can hope that by analogy with cholesterol and statins, the development of feasible strategies for prevention based on mechanisms discovered through genetics might be possible for some common variants with high attributable risk. Speculating further, multiple genomic variants and environmental risk factors may combine to perturb cellular regulatory networks, which in turn perturb cellular phenotypes and lead to susceptibility²⁷. If so, dietary or lifestyle means might be found that counteract the perturbation and provide a rational 'physiological' approach to prevention.

K.S. The age of the individual when the genomic information is gathered has an effect on the information's usefulness: the younger the individual, the greater the potential usefulness. It would probably be best to have this information in the hands of both the individual and the health-care system. In the health-care system, it is probably wise to keep the information under the individual's name and social security number for the delivery of health care and anonymously for the purposes of research and generating health-care statistics, where and when that is appropriate.

Q *What are the barriers to making the most of this potential?*

A.E.G. To use personalized genomic information effectively, we first need to understand what it means. To know that someone has a specific genetic variant (let alone a collection of variants) is of limited benefit without a sound understanding of the real-world implications of the variant. Therefore, we need to understand the biology of what the variant does. Moreover, for most 'personalized health care', we need also to know how an individual's knowledge of having the variant will affect his or her personal health attitudes and, more importantly, health behaviours. Then we need to understand how those health behaviours, and other genome-based health interventions, will affect health outcomes. A further barrier is educating the health-care workforce about both the science of genomics and how to apply it effectively in clinical settings. This will require multiple, concerted efforts aimed at a wide variety of health professionals, both in training and in practice²⁸. Similar efforts are needed to increase the public's 'genetic literacy'²⁹.

As difficult as these challenges are, perhaps the greatest barrier is fully understanding gene-gene and gene-environment interactions. To acquire that knowledge will require much creative research; to apply it will revolutionize health care.

A.L.M. The biggest barrier to making the most of personalized genomic information is our limited understanding of its functional significance and its relationship to epigenetic factors, including environmental contributions to health and disease. As our understanding increases, there will be additional barriers to its successful clinical integration. It will eventually become more economical to generate whole-genome sequences than to order targeted tests for single-gene disorders. Analysis and interpretation of this vast amount of data has already proven to be a challenge in the research context; it is not likely to be any easier for the busy clinician. Identifying information that may be of clinical significance to the individual patient will be impracticable without the use of automated systems and clear guidelines. There are not enough clinical geneticists to help patients interpret whole-genome sequencing results, and research shows that primary-care physicians lack the knowledge and expertise to help patients understand even single-gene genetic test results²⁸; they certainly are not prepared for whole-genome counselling.

Finally, the current US reimbursement system is not designed to cover the costs of integrating personal genomes into routine clinical care, which will require extensive counselling and patient education. In the context of the health-care reform debate in the US, the implications of personalized genomics in terms of cost, access and quality of care must be considered.

B.P. In terms of gene discovery, only a small proportion of the genetic variance of disease risk has so far been identified. Affordable re-sequencing may reveal rare variants, but there may be a long 'tail' of effects so small that they will be detectable only in combination, through their effects on phenotypes. Furthermore, to derive the risks that are associated with certain genes and to provide interventions that are based on their mechanisms of action, we will need to understand how genes interact with each other and with the environment in a mathematical and mechanistic sense,

Demonstration of benefit will also be important. Many of the applications of personalized genomic information will involve targeted screening and prevention. The assessment of such interventions is notoriously difficult, requiring careful design, large numbers and long follow-ups. The incorporation of genomic information will require new studies, which will rapidly be overtaken by new gene discoveries. These studies must be able to address issues of overall benefit, public understanding and acceptance, as well as lives saved.

Finally, there are issues of understanding. Screening based on risk (for example, age, family history and smoking history) is commonplace but perhaps not commonly perceived as such. The widespread use of genetic testing will draw not only scientific but also public attention to the ideas of risk categories and access to medicine. Beyond the expected issues of uptake and confidentiality, we must ascertain how the public will respond to this. Knowledge of increased risk may create expectations of medical interventions that may not match either what can be provided or what is medically possible. Knowledge of lower risk may induce false reassurance and missed opportunities for prevention, and the public may find it hard to accept the withdrawal, on grounds of reduced risk, of previously available screening. Education both of the public and of policy makers will be needed.

K.S. There are several barriers to making the most of the potential that lies in personal genomics information. One is the difficulty in getting our society to pay for 'population screening' and subsequent preventive measures, although I believe that the arrival of personal genomics information will eventually drive the acceptance of both. Another barrier is the perceived complexity of genetics. A third barrier is the concern that personal genomics information may be used to discriminate against people. A fourth lies in the conservative attitude of the medical profession, which is inclined to want to control the access that individuals have to information about their health and disease. Somehow the medical profession seems to believe that in some instances it may be more dangerous to know than it is not to know about the risk you have of diseases.

Alan E. Guttmacher is at the National Institute of Child Health and Human Development, 31 Center Drive, Room 2A03, Bethesda, Maryland 20892-2152, USA.
e-mail: guttmach@mail.nih.gov

Amy L. McGuire is at the Center for Medical Ethics and Health Policy, Baylor College of Medicine, Room 310D, One Baylor Plaza, Houston, Texas 77030, USA.
e-mail: amcguire@bcm.edu

Bruce Ponder is at the Cancer Research UK Cambridge Research Institute, Li Ka Shing Centre, Robinson Way, Cambridge CB2 0RE, UK.
e-mail: bruce.ponder@cancer.org.uk

Kári Stefánsson is at deCODE genetics, Sturlugata 8, IS-101 Reykjavik, Iceland.
e-mail: hstefans@decode.is

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Competing interests statement

Kári Stefánsson declares competing financial interests: see Web version for details.

DATABASES

Entrez Gene: <http://www.ncbi.nlm.nih.gov/entrez/seq.fcgi/10005495>
BRCA1

FURTHER INFORMATION

Alan E. Guttmacher's homepage: <http://www.genome.gov/10005495>
Amy L. McGuire's homepage: <http://www.bcm.edu/ethics/?pmid=3835>
Bruce Ponder's homepage: <http://www.cambridgecancer.org.uk/research/loc/cambridge/ccri/ponderb/?view=CR1&source=research>
Kári Stefánsson's homepage: <http://www.decode.com>

23andMe: <https://www.23andme.com>
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