Genomic medicine: genetic variation and its impact on the future of health care

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Advances in genome technology and other fruits of the Human Genome Project are playing a growing role in the delivery of health care. With the development of new technologies and opportunities for large-scale analysis of the genome, transcriptome, proteome and metabolome, the genome sciences are poised to have a profound impact on clinical medicine. Cancer prognostics will be among the first major test cases for a genomic medicine paradigm, given that all cancer is caused by genomic instability, and microarrays allow assessment of patients' entire expressed genomes. Analysis of breast cancer patients' expression patterns can already be highly correlated with recurrence risks. By integrating clinical data with gene expression profiles, imaging, metabolomic profiles and proteomic data, the prospect for developing truly individualized care becomes ever more real. Notwithstanding these promises, daunting challenges remain for genomic medicine. Success will require planning robust prospective trials, analysing health care economic and outcome data, assuaging insurance and privacy concerns, developing health delivery models that are commercially viable and scaling up to meet the needs of the whole population.

Keywords: genomic medicine; gene expression profiling; microarrays; proteomics; metabolomics; personalized health care

1. INTRODUCTION

Of all the promises of the current scientific and social revolution stemming from advances in our understanding of the human genome, genomic medicine may be the most eagerly awaited. The prospect of examining a person's entire genome (or at least a large fraction of it) in order to make individualized risk predictions and treatment decisions is a tantalizing one. Since the completion of the draft sequence of the human genome (Lander *et al.* 2001; Venter *et al.* 2001), the idea of using information derived from genome analysis to tailor care to individual patients has gained prominence (Ginsburg & McCarthy 2001; Meyer & Ginsburg 2002; Snyderman & Williams 2003; Bentley 2004; Thrall 2004). The opportunity is enormous: for the first time, we are in a position to characterize health and disease states by their molecular fingerprints, develop meaningful stratifiers for patient populations, elucidate mechanistic pathways based on genome-wide data and develop new preventive, diagnostic and therapeutic strategies that will shift the focus of care from intervention to prevention.

Having access to the entire human sequence is a necessary but insufficient prerequisite for genomic medicine. What is equally important is having the technology at hand to reliably visualize individual genomes (and their derivatives, the transcriptome, proteome and metabolome; see table 1) for health and disease status. Each of these technologies provide

information that, in combination with clinical data, can contribute to assessment of individual risks and guide clinical management and decision-making (figure 1). Large-scale genotyping of single nucleotide polymorphisms (SNPs) is one such technology; assaying genotypes at thousands of loci can provide a personalized signature of health or disease. The DNA microarray is another technology, the power of which resides in its ability to measure the expression level of thousands of genes simultaneously. In doing so, it generates a molecular signature and can define a particular phenotype (Chung *et al.* 2002; Mariadason *et al.* 2003). Because cancer tissue is accessible and amenable to RNA profiling, and as cancers are characterized by heterogeneity and complexity, 'molecular portraits' of individual tumours offer the potential for the individualization of cancer diagnosis, prognosis and treatment (Nevins *et al.* 2003).

Genomic complexity is reflected at the DNA and gene expression levels. Proteomics—the analysis of the entire protein content of a cell or tissue via multiple technologies—is another approach that will be essential in bringing personalized health care to fruition (Rees-Unwin *et al.* 2004; Weston & Hood 2004). At the end of the biochemical pathway lies metabolomics, another breakthrough technology that allows physicians and investigators to visualize the inherent biological complexity of small molecule metabolites on a large-scale in the serum or other biological fluids from patients. Metabolomics is the *ex post facto* component of genomic medicine (Schmidt 2004).

The undeniable allure of genome technology as applied to medicine is high. But what of the realities of bringing genomic medicine to the clinic and seamlessly

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Table 1. Personalized signatures of health or disease.

dataset ('omic' approach)	technology platform or approach
human genome sequence (genomics)	single nucleotide polymorphisms (SNPs)
gene expression profiles (transcriptomics)	microarrays of ~20 000 gene transcripts
proteome (proteomics)	protein arrays of specific protein products
metabolome (metabolomics)	analysis of hundreds to thousands of metabolites

Figure 1. Schematic overview of model for genomic medicine based on integration of gene expression profiles with clinical and other data. Based in part on Nevins *et al.* (2003).

integrating it within current models of health care delivery? This is where the steepest barriers lie. While the human genome sequence is now available, it is important to acknowledge that our knowledge of the genome and its biological complexity is nowhere near complete, and installation of genomic protocols into standard clinical care is virtually *terra incognita*. There are a host of clinical, economic, insurance, privacy and commercialization concerns that will need to be addressed and that vary substantially among different countries. And of course, before we can confront those, we must be certain that genomic medicine is on the soundest possible scientific footing. If those issues can be dealt with systematically, the prospect of using genomic information to offer patients' health care that is truly prospective in nature may finally be within our grasp.

In this overview of genomic medicine, we review the major likely contributions of several genome technologies to both current and future health care. We then present a model for an integrated genomic medicine approach that will likely be necessary to fully incorporate principles of genome analysis into the delivery of health care.

2. USING SNPs IN GENOMIC MEDICINE APPLICATIONS

As of early 2005, nearly 10 million SNPs had been deposited in the National Center for Biotechnology Information's public SNP database, dbSNP (Wheeler *et al.* 2005), of which an estimated three to five million were likely to differ between any two individuals (Shastry 2002; Altshuler & Clark 2005). Because SNPs are binary, they are especially amenable to large-scale and high-throughput typing (Twyman 2004; Hinds *et al.* 2005). Consequently, SNP typing is a much faster way to assess DNA differences among individuals than DNA sequencing.

It is clear that inherited genetic differences among individuals can cause differential responses to medications (Goldstein *et al.* 2003; Tate & Goldstein 2004). The study of the relationship between genetic differences and drug response is known as 'pharmacogenetics' (although, as more loci are incorporated into such studies, the field is increasingly referred to as 'pharmacogenomics'). Some patients respond to medications with few if any side effects; others fail to respond and may experience serious adverse reactions. A recent multicentre British study found 6.5% of hospital admissions to be related to adverse drug reactions (ADRs; Pirmohamed *et al.* 2004). A 1998 meta-analysis suggested that ADRs may be responsible for more than 100 000 deaths per year in the US (Lazarou *et al.* 1998). Pharmacogenomics will be among the leading edge of applications of genomics to medicine (Ahmadi *et al.* 2005).

In the future, SNPs will likely have other uses in genomic medicine, especially in diagnostics and presymptomatic testing. As most SNPs reside in non-coding DNA, they are unlikely to cause disease directly. However, there are exceptions, and both synonymous and non-synonymous variants in genes have been implicated in a variety of disorders (Emonts *et al.* 2003; Worthington & John 2003; Imahara & O'Keefe 2004; Garcia-Barcelo *et al.* 2005; Hawn *et al.* 2005). In addition, SNP patterns—just like individual polymorphisms used in conventional Mendelian linkage studies—may be strongly associated with diseases. In complex diseases such as diabetes and heart disease, SNPs from multiple genes with weaker effects may be analysed in parallel and used to generate quantitative risk assessments.

The complexities of both SNP typing and study design are especially evident in behavioural disorders. In 2003, researchers showed that a single SNP in the μ -opioid receptor gene had a measurable clinical impact on problem drinkers trying to stay sober (Oslin *et al.* 2003). This variant increases the μ -opioid receptor's affinity for β -endorphin threefold. The presence of alcohol increases β -endorphin levels, thereby prompting μ -opioid receptors to produce a reward sensation. In a *post hoc* analysis of alcoholics, Oslin *et al.* found that 48% of individuals without the SNP relapsed into heavy drinking versus just 26% of those with the variant. Presumably, because the variant in the μ -opioid receptor gene causes the receptor to hold onto its β -endorphin more tightly, those alcoholics with the variant are less compelled to use alcohol to increase their endorphin levels.

What are the consequences of this for treatment of alcoholics? For the last decade, psychiatrists in the US have had approval from the Food and Drug Administration to prescribe naltrexone—a μ -opioid receptor

antagonist—for the treatment of alcohol dependence. Unfortunately, as many as 40% of the patients fail to remain alcohol-free under naltrexone regimens (Kenna *et al.* 2004). SNPs such as the one discovered by Oslin *et al.* are good candidates to be a major reason why. If we knew ahead of time which patients were more likely to benefit from naltrexone, we might proceed more aggressively in treating that population with naltrexone and look for other solutions for those problem drinkers with naltrexone-unresponsive genotypes.

Similar examples have been documented for SNPs in other genes or groups of genes associated with drug response. In cardiovascular disease, we now know that SNPs in the angiotensinogen, apolipoprotein B and alpha-2 adrenoreceptor genes can predict the changes seen in left ventricular mass during antihypertensive therapy with beta blockers (Liljedahl *et al.* 2004). Elsewhere, polymorphisms in genes that encode drug metabolizing enzymes, drug transporters and drug targets can have profound implications for pharmacotherapeutics (Sakaeda *et al.* 2004). Among the most well-characterized example is P-glycoprotein/*MDR1*. More than 50 alleles of this gene have been shown to have a direct impact on the pharmacokinetic profiles of multiple drugs (Ishikawa *et al.* 2004). Other drug metabolism polymorphisms can have profound clinical consequences. Thiopurine methyltransferase (TPMT), a cytoplasmic, evolutionarily conserved and fairly ubiquitous enzyme, catalyzes the S-methylation and inactivation of thiopurine drugs such as 6-mercaptopurine (6MP; Weinshilboum 2001, 2003; Cara *et al.* 2004). 6MP is used to treat acute lymphoblastic leukaemia as well as inflammatory bowel disease (Van Scoik *et al.* 1985). Persons homozygous for *TPMT* alleles that render them deficient in the enzyme (approximately 1 in 300 Caucasians) are at a higher risk of life-threatening adverse effects if treated with standard doses of thiopurines (Collie-Duguid *et al.* 1999).

3. GENE EXPRESSION PROFILING IN PREDICTING CANCER RECURRENCE

Without question, remarkable progress has been made in the fight against cancer. A number of conditions—acute lymphocytic leukaemia, Hodgkin's disease and testicular cancer, for example—are now clinically manageable chronic conditions, thanks to improvements in diagnosis and the development of powerful new chemotherapeutic agents. But while cancer death rates have fallen in recent years, malignancies have recently achieved the dubious distinction of supplanting heart disease as the number one cause of mortality in the US for those under the age of 85 (Jemal *et al.* 2005).

The difficulty of making a significant reduction in cancer death rates stems directly from the fact that the word 'cancer' is itself a misnomer, implying a single homogeneous entity, when in reality it is exactly the opposite. Cancer is intrinsically heterogeneous. Two women may carry identical mutations in the *BRCA1* gene and develop metastatic carcinoma, yet they may differ in tumour size, basal phenotype and the number

of axillary lymph nodes to which their tumours spread (Narod & Foulkes 2004). In order to capture that heterogeneity and use it to develop individualized prognostics and treatment regimens for cancer patients, a growing cadre of investigators have begun to use microarray-based gene expression analysis as the centrepiece of a strategy to use genome-based information in assessing individual risks (figure 1; Nevins *et al.* 2003; Wulfkühle *et al.* 2004).

Breast cancer is one of the most salient examples. The current approach to breast cancer diagnosis typically involves assessment of (i) lymph node involvement, (ii) oestrogen receptor status and (iii) tumour size. Expression of the oestrogen receptor is associated with a better clinical outcome, while lymph node-negative malignancies are associated with a more favourable prognosis (Schnitt 2001). Even in state-of-the-art facilities, molecular analysis of most breast tumours include no more than a few of the usual candidates: hormone receptors, DNA ploidy, the *HER2/NEU* oncogene and the tumour suppressor gene *p53* (Masood 2000).

Gene expression profiling in breast cancer has begun to provide a more sophisticated molecular picture and allow for individualized recurrence risks. A 70 gene signature designed to predict patient survival is already being marketed in Europe (van 't Veer *et al.* 2002; Hamilton 2004). More recently, other investigators have refined gene expression profiling by utilizing alternative analytic approaches and/or by incorporating multiple pieces of clinical data such as age, tumour characteristics and hormone receptor status in their recurrence risk models (Glinsky *et al.* 2004; Pittman *et al.* 2004). By using amalgamated data in a set of Bayesian analyses, it has been possible to generate truly individualized probabilities of disease outcome in breast cancer as opposed to simpler binary stratification schemes that only place women into 'poor' versus 'good' prognostic categories (Pittman *et al.* 2004).

The clinical utility of such profiling is clear. An elderly breast cancer patient with a low risk of recurrence may very well opt to forego a harsh round of chemotherapy, if such an option would extend her life but substantially reduce its quality. In other cases, a high risk of recurrence may indicate that prophylactic chemotherapy or surgery could be beneficial and worth the risk.

While the breast cancer data to date are impressive, definitive validation of the approach will require large prospective clinical trials. In 2004, a consortium of European and Latin American researchers launched a randomized clinical trial for the use of microarrays to help determine appropriate therapies for lymph node-negative breast cancer patients (Hamilton 2004). It is expected that a systematic clinical trial aimed at validating gene expression profiling in breast cancer will be launched at several US institutions in 2005.

4. PROTEOMICS AND PERSONALIZED MEDICINE

Proteomics is the study of the entire protein complement resident in organs, tissues and/or individual cell types; like genomics, it takes a global, system-wide view

of the organism (Hood 2003). Proteins are among the ultimate products from the human genome. While total proteome size is difficult to estimate, the human proteome may contain more than 90 000 different proteins (Harrison *et al.* 2002), some four to five times the number of genes in the genome. Diversity at the level of the proteome is due to extensive RNA splicing and to post-translational modifications such as glycosylation, prenylation and myristoylation (Khidekel & Hsieh-Wilson 2004). The advantages of assessing the serum or plasma proteome over other 'omics' approaches (table 1) is that it is accessible (via blood testing, for example), which is an important feature for developing and measuring biomarkers of disease states and developing risk predictors. There is no doubt that whole-proteome approaches will yield an important new set of predictors when applied to diverse physiologic states such as heart failure and acute coronary syndromes where proteins are already being used for diagnostics on a limited scale (reviewed in Loscalzo 2003; Bukowska *et al.* 2004).

Cardiovascular medicine has been using protein markers in diagnosis for years. For example, myoglobin and creatine kinase are used as indicators for myocardial infarction, while LDL and apolipoprotein B are indicators of atherosclerosis. More recently, proteins have enabled more precise diagnosis of congestive heart failure with B-type natriuretic peptide and N-terminal B-type natriuretic peptide. A growing number of protein determinants of risk for acute coronary syndrome are emerging: cardiac troponin I, C-reactive protein, interleukin-6, myeloperoxidase, tissue factor, monocyte chemotactic factor 1, pregnancy-associated plasma protein A, albumin-cobalt binding, CD40 ligand and heart-type fatty acid-binding protein have all been recently associated with myocardial infarction and/or cardiac ischaemia in cross-sectional studies (reviewed in Abbate *et al.* 2003; de Lemos & Morrow 2003; Kullo & Ballantyne 2005). In the coming years, it is likely that a protein biomarker panel will be available that measures homeostasis, platelet function, inflammation status, necrosis and haemodynamics that will allow tailoring of therapeutics in the acute setting. Similar to the growing impact of gene expression microarrays discussed above, it may be the *pattern* of markers that is more revealing diagnostically or prognostically than the mere presence or absence of a particular protein marker.

Perhaps even more than genomic analysis, successful proteomic applications are a function of multiple technology platforms. While a comprehensive review is beyond the scope of this paper, the general approaches will be covered in brief. Traditional methods of protein analysis, including gel electrophoresis in one or two dimensions and mass spectroscopy (MS), tend to require large sample quantities and labour-intensive preparation. To improve upon these, investigators have sought to couple protein separation and enrichment to MS, tag and label protein mixtures to highlight differences between test and control samples, increase the resolution of gel electrophoresis, develop laser microdissection techniques to study cell populations directly and construct protein microarrays that can

generate profiles of known signalling pathways or tissue-specific networks (reviewed in Liotta *et al.* 2001).

As with gene expression profiling, cancer will likely be the first disease that experiences the widespread clinical application of proteomics. This makes intuitive sense: gene expression profiles may not always correlate with the functional state of human proteins, which may be extensively translationally or post-translationally modified. In addition, DNA microarrays cannot offer information regarding protein-protein interactions or how cellular networks might function *in vivo* (Wulfschuhle *et al.* 2004). Thus, proteomic analyses complement gene expression profiles. Proteomic approaches have taken two major directions: one in which *patterns* of protein expression as biomarkers are generated by surface-enhanced laser desorption/ionization time-of-flight (TOF) MS (Seibert *et al.* 2004) and the other where complex protein mixtures are deconvoluted by various separation techniques combined with LC/MS to *identify* specific protein biomarkers. The former technique is conceivably simpler to apply, but at least in the case of developing a diagnostic for ovarian cancer has failed to produce reliable and reproducible results (Petricoin *et al.* 2002; Diamandis 2004; Garber 2004). The latter techniques, while more laborious, are likely to stand the test of time because of the ability to examine the biology of the protein(s) discovered and translate the results to more conventional protein assays such as ELISAs. Regardless of which technology is used, it will undoubtedly be the case that *multiplex* protein biomarker analyses will be the standard as opposed to the current one-protein-at-a-time approach to diagnostics. The large regulatory gap involving genomic and proteomic tests can only be bridged with extensive, reproducible datasets and a firm set of standards for validating and regulating these types of tests (Ransohoff 2005).

5. APPLICATIONS OF METABOLOMICS

Metabolomics resides at the end of the biological road that commences with DNA. It is the place where the variation in genomes, both static and expressed, become integrated. Metabolomics—the study of metabolite profiles in biological samples—will be an integral part of the broader spectrum of genomic medicine (table 1). Its goal is to relate the physiological consequences of disease, i.e. the metabolites associated with pathological processes, to those diseases' genomic origins. Metabolite profiles can offer unique insights into cellular physiology and the environment in which that physiology takes place.

Without question, the most mature metabolomics' application is the use of biomarkers as diagnostics and indicators of disease progression. Measurement of blood glucose levels in diabetes mellitus and serum cholesterol in cardiovascular disease has been a staple of general medical practice for a long time. However, just as single-gene testing cannot provide more than a glimpse of a single aspect of a patient's health, single-metabolite measurement cannot serve as anything more than a crude proxy for the physiological activities of billions of cells and the organs they populate. The challenge for metabolomics—as for

proteomics—will be to move to the realm of multiplex testing and high-throughput screening of hundreds or even thousands of metabolites akin to the way microarrays are now used to examine the activity of thousands of genes simultaneously.

As in proteomic analysis, one of the key tools in metabolomics is MS (de Hoog & Mann 2004). Both MS and the other principal method of examining metabolites, nuclear magnetic resonance (NMR), are well-established platforms already resident in most hospitals. Each has its advantages. NMR requires relatively little sample processing, preserves sample integrity and can rapidly identify and localize abundant analytes in a sample with fairly high accuracy. MS can quantify individual components within a sample and allow simple spectral analysis when coupled with gas or liquid chromatography. Newer TOF MS technology has reduced analysis time to just a few minutes (Guttman *et al.* 2004).

The rate-limiting technology in metabolomics may be bioinformatics. In contrast to genome databases, most metabolomics databases and analysis software remain either *ad hoc* or proprietary and, if access is available at all, it is typically expensive (Adams 2003). For metabolomics to penetrate clinical practice in a tangible, reimbursable way in the US, both new analytical resources and innovative cost-containment approaches will need to be developed. Recently, there has been encouraging signs that practical, web-based bioinformatics tools for metabolomic analysis are starting to become available on a more widespread basis (Arita 2004).

One of the keys to efficacious applications of metabolomics in the clinic will be the reproducible correlation of metabolite data with other established clinical measurements. Diseases where metabolites are readily available and pathology practices have been standardized would appear to offer the best opportunities. Prostate cancer, for example, is a case where computer-aided image analysis of pathology slides may be used to generate diagnostic correlations between quantitative pathology measures and metabolite profiles (Burns *et al.* 2004). Infectious disease applications also hold promise. Recent work demonstrated the feasibility of using NMR to distinguish between avirulent laboratory and highly pathogenic clinical strains of *Bacillus cereus* based solely on their metabolic profiles (Bundy *et al.* 2005).

Serum cholesterol measurement remains the best example, albeit a crude one, of metabolomics in the clinic. It is truly prospective in nature and thus provides proof-of-principle that one can measure a metabolite and offer useful advice and information to a patient otherwise deemed healthy (Watkins & German 2002). The cholesterol paradigm must now be globalized in order to allow assessment of the thousands of metabolome constituents in a single assay, just as gene expression technology has been scaled-up using microarrays and comparative genomic hybridization technology. If metabolomics can be scaled-up and the approach coupled with family history, clinical and genomic information, it can become yet another tool in the physician's expanding arsenal to be used in the delivery of personalized health care.

6. AN INTEGRATED MODEL OF GENOMIC MEDICINE

The dynamics of the American health care industry is at least as complex and opaque as any transcriptional network or multimeric protein. Nevertheless, several trends appear to be pointing towards the development of a model for personalized medicine, within which genomics can be expected to figure heavily:

- (i) US consumers are being asked to shoulder an ever growing share of their health care costs (Goff 2004). It has been suggested that by exposing health care to even greater consumer pressure, market forces will expand choices and presumably, options for individualized care (Herzlinger 2002).
- (ii) Thanks to the Internet, these same consumers are more informed than ever about their own health and the broad range of choices available to them, both in terms of clinical care (O'Connor *et al.* 2003) and insurance benefit options (Bundorf *et al.* 2004).
- (iii) The pharmaceutical industry, mired in a long slump, is under siege from reports of ADRs, patent expirations exposing blockbusters to generic competition, complaints about pricing, a protracted and expensive development process and declining numbers of new drug approvals (Angell 2004; Williams 2004; Maxwell & Webb 2005).
- (iv) At the same time, advances in biotechnology—in the form of genomics, proteomics, metabolomics, imaging technologies, bioinformatics and novel devices such as biosensors—are providing myriad opportunities to take a systems biology approach to treating individuals and thereby change the face of clinical care (Morel *et al.* 2004).

If these are the forces that are poised to drive the adoption of personalized health care, the question remains as to how genomic medicine can be integrated into that model (Snyderman & Williams 2003). The answer is likely to be neither easy nor straightforward. Rather, as illustrated in figure 2, to make genomic medicine truly *translational*—to traverse the great distance from bench to bedside—will require methodical, systematic steps rooted in evidence-based science and clinical acumen. Initially, meticulous data and sample collection will be paramount. With samples in hand, practical testing of the genomic, proteomic and metabolomic approaches described here becomes critical. More than ever, human biology (and its impact on health) is now a quantitative information science; consequently, robust computational methods for judging and interpreting 'omic' data in a way that is meaningful to scientists, clinicians and patients must be developed. Subsequently, genomic approaches must be validated for their clinical utility in large, multicentre trials. Once the technology infrastructure is in place and the methods validated, clinician involvement becomes utterly essential. For example, can a general practitioner in a small, remote town interpret a proteomic test? Has the patient been well served by

Figure 2. Integrated translational process for genomic medicine.

the process? How will we quantify that? What should our expectations be?

Ultimately, successful implementation of a genomic medicine approach will be an iterative process. Thus, it will be imperative for research and clinical scientists as well as policy experts to perform ongoing outcomes research, adjust the existing model based on the results of that research, and re-evaluate the process *ad infinitum*.

Some of the most challenging of these iterations will be on the policy side. In March 2005, the US Food and Drug Administration released its 'final' guidance on pharmacogenomics data submissions (<http://www.fda.gov/bbs/topics/news/2005/NEW01167.html>). This represents a major step towards paving the way for a new generation of diagnostics and therapeutics based on an understanding of disease at the molecular level enabled by genomic medicine. Commercial developers of genome technology are also responding to the opportunities presented by advances in the various other omics technologies. Given the US's fragmented health care system, devotion to free enterprise, high percentage of gross domestic product committed to health expenditures and high standard of living, the US likely represents the most fertile market for private genomics enterprises (Reinhardt *et al.* 2004). But technology development does not equal technology adoption. Genome technology, like microprocessors, has become dramatically cheaper, but it remains to be seen exactly where the 'tipping point' is with regard to public health. Clinical trials to determine safety and efficacy will not be sufficient. Clinicians, pharmacists, economists, epidemiologists and operations researchers must also be engaged in assessing costs and benefits. In order to truly evaluate cost effectiveness, strict criteria must be established *a priori* (Higashi & Veenstra 2003).

In a broader context, society at large must grapple with the price of health care in the genomic age. How will we allocate amazingly powerful but limited resources in a just and equitable way? Answering that question may require human advances even more dramatic than the technological breakthroughs that

have marked the beginning of genomic medicine. It will be incumbent upon those of us arguing the benefits of the Genome Revolution to see it through to the end.

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