Summary

Genomic medicine will clearly revolutionize the practice of medicine. Medical genomics makes patients the ideal experimental subjects. For good reasons at the time, governments turned away from clinical research in the 1960s, preferring to focus on mechanistic studies in subhuman model systems. Clinical research was left to the research pharmaceutical industry. Unfortunately, the research pharmaceutical industry is on its last legs, and is in no position to develop genomic medicine.

To take full advantage of genomic medicine, the NHS will have to take a leadership role. Every GP will need to participate in a quality improvement (QI) program to better his or her patient outcomes. The existing technology is adequate. Because the research pharmaceutical industry already has more targets than it can handle, the NHS may need to become a "virtual" pharmaceutical company itself.

There will be obvious rewards, in terms of revenues and clinical outcomes, if the NHS takes such a proactive approach.

Introduction

The House of Lords Science and Technology sub-committee on genomic medicine is quite correct in believing that genomic medicine is a new field that could have tremendous impact on the daily practice of medicine. The sub-committee's questions, reproduced below, are thoughtful. But they presume a rosier picture than actually exists.

The experience of a practitioner who still sees patients (as a general internist) and CEO of a medical genomics company may be valuable for the sub-committee to consider.

My comments are based on 15 years' of wandering in the desert of genomic medicine (1-11). It has been a desert in every sense of the word: there has been virtually no research funding, no professional or academic collaboration, and no business model. And, of course, there is no scientific precedent—those in the field are making it up as we go along. The sub-committee's questions about "regulation" make it clear that you understand that.

There is no doubt that genomic medicine will revolutionize the practice of medicine, sooner or later. So far, the medical establishment has managed to make it later (9).

The medical system, like any highly lucrative industry, profits from the status quo. Genomic medicine, by revealing the map for common diseases, makes it simple to inhibit disease pathways. It is certainly not rocket science! If over activity of an enzyme such as angiotensin I-converting enzyme (ACE) is behind a disease (2), then using an ACE inhibitor should help. Indeed, it does (1,5,7,10).

Genomic medicine already makes it possible for ordinary GPs to conquer diseases which still baffle government and non-profit funding agencies.

Most common diseases could be solved in the next few years. However, if the medical establishment has its way, they won't be. Clinical outcomes won't improve, but a few labs in a few prestigious universities will continue to be awarded enormous funds to perform mind-boggling but irrelevant tours de force, such as sequencing tumor genomes.

Today's news illustrates the trend perfectly: http://www.genomeweb.com/issues/news/146282-1.html. The Wellcome Trust will spend

USD 60 million on whole genome association studies using the Affymetrix 1 million SNP (single nucleotide polymorphism) chip. This, notwithstanding the fact that earlier versions of Affymetrix's chip containing 100K, 300K, 500K, and 600K SNPs haven't worked, and that linkage techniques haven't worked for polygenic diseases for the past 25 years (see below).

An alternative future

It is already possible, using the right fishing net, to find thousands of disease-associated SNPs. In 2004, we found roughly 5,000 SNPs for each of six different cancers in whites (Caucasians): breast, colon, lung, ovary, pancreas, and prostate. That was with a fishing net of some 20,000 SNPs that covered one-third of the genome. We now have a SNPnet™ of 80,000 SNPs that covers the entire human genome.

It must be said, however, that our SNPs come from a public database (dbSNP), and so apply only to Caucasian patients. To find SNPs for other ethnic groups—people of African ancestry, Asians, and mixed populations such as Brazilians—will require the construction of a separate dbSNP for each ethnic group.

The SNPs that we found are mostly located within 10 kb of a discrete gene. The disease-associated version of the SNP (susceptibility allele) presumably causes differential gene expression relative to the protective allele: over expression of oncogenes, under expression of tumor suppressors.

The traditional, mechanistic model of biomedical research would next require the construction of promoters containing the SNP, linked to reporter genes such as luciferase or CAT, in order to test exactly what the SNP does in various model systems. This could easily take 3-5 years and several hundred thousand pounds per SNP. Afterwards, the gene affected by the SNP would be explored for its role in tumorigenesis. This could easily take decades. For example, the role of BRCA1 and 2 is still not understood more than a decade after their discovery. The same is true for the CF gene, the PKD gene, etc. Discovery of these genes hasn't yet led to drugs for treating patients.

Let us agree at the outset that the first goal of genomic medicine is improvement of clinical outcomes. Let us also agree that time is of the essence. Ultimately, a disease-causing gene is only significant if inhibiting it has a positive effect on the disease.

Genomic medicine provides so many good targets that one can skip the promoter-bashing experiments mentioned above, and race ahead to designing drugs. Those with the lowest toxicity/efficacy ratio can be tested in animal models, without bothering to work out the exact cellular mechanism involved. That can be left to academic labs able to devote time to the subject.

In other words, the NHS can push for better clinical outcomes, while the MRC continues to fund basic research into mechanism.

An alternative focus: QI

Quality improvement (QI) is still missing from healthcare. In most industries, research is intimately tied to QI. Not so in medicine. Since 1948, as research has gotten more basic and less clinical, progress in clinical medicine has ground to a halt. More progress was achieved in medicine in the 1930s, arguably, than in all the years since the War on Cancer was declared in the US by President Nixon in 1972. Cancer survival rates have not improved for most common adult cancers. Nobody understands why stomach

cancer rates have been falling. The decrease certainly can't be duplicated yet in other cancers.

The House of Lords Science and Technology sub-committee has a historical opportunity to use genomic medicine as a tool to improve quality in the NHS. The tool is certainly reliable enough. It will mean better patient outcomes and lower costs immediately—5% within the first 12 months of adoption, with greater savings over time.

Cardiovascular disease can already be delayed, if not arrested (1,2). The remaining frontiers are oncology, followed by neurodegenerative diseases and crippling psychiatric diseases like schizophrenia and autism.

The NHS could use its unique resources to create the molecular diagnostics and genomics-based therapeutics of the next century or two. This would provide a revenue stream (river, really) for the NHS just when it needs fiscal help the most: as the Baby Boomers age and rely on it more heavily.

Molecular Diagnostics

The 5,000 SNPs we've already found for six cancers in whites are sufficient to predict 2/3 of cancers in whites. Little additional work is required—perhaps GBP 1.5 million over a 3 year period—to achieve FDA approval. A prospective trial could be performed at little cost over the next 5-10 years demonstrating that early diagnosis could actually lower cancer mortality.

ACE inhibitors or ARBs could be tried to delay or even prevent tumor growth (2) in patients detected to be at high risk for a particular cancer. So could one or more existing medications directed at some of the thousands of oncogenes we have already discovered.

In addition, already established radiological techniques (ultrasound, MRI) could be used to identify tumors while they were still small and surgically resectable for a cure.

Therapeutics

Until now, pharmaceutical companies have identified a disease pathway and then found inhibitors to interfere with the pathway. The emphasis has been on efficacy. Toxicity only becomes an issue later. This is backwards, since 99.9% of efficacious drugs fail because of toxicity. From a business point of view, this approach has been disastrous. The cost of bringing a new drug to market is now USD 1 billion and 12 years; it is only going up.

The few remaining research pharmaceutical companies can no longer tolerate any failure. They eschew basic science, instead asking biotechnology companies to present them with Phase III-approved drugs.

The only problem is that it costs GBP 250 million to get through Phase III. Nobody in their right mind would invest that much in a biotech company. Biotech companies are one-trick ponies whose drugs fail at the rate of 99.9%, the same failure rate as Big Pharma (research pharmaceutical companies).

With medical genomics, many thousands of participating genes can be identified at once. If one believes in the power of genomic epidemiology, then one can assume that most, if not all, of the associated genes are causative, as we have found for ACE (1-11). In other words, one can take efficacy for granted. Then one can screen out molecules based on toxicity. 99.9% of compounds will continue to fail because they are too toxic.

The 0.1% of compounds that pass toxicity assays can then be worked up for clinical trials. Starting with 3,000 drugs directed against 3,000 different targets should still result in 3 satisfactory drugs. Genomics can take the failure out of the pharmaceutical industry, and restore its pipeline.

Note that genotyping patients in order to market a toxic drug is a bad idea. It is much less expensive to discard a drug because of toxicity in an early in vitro assay than to (a) establish its mechanism of toxicity in humans; (b) find the human genetics behind this toxicity; (c) validate the toxicity test in a patient population, and (d) try to recoup all of the additional research costs by charging extra for the drug.

It still takes many years to bring a new chemical entity to market. In the meanwhile, already existing drugs can be repurposed, perhaps in combination. The genes associated with the disease determine which drugs to try. So many thousands of genes are involved with each disease that it's already possible to find several dozen known drugs, with established toxicity profiles.

Stage IV cancer patients, whose prognosis is grim, could be used to test cocktails of already existing, non-toxic drugs. Cocktails may work better than single agents. Blocking multiple steps partially may limit the overall flux through the disease pathway specifically, effectively, and without toxicity, the goals of "kind" chemotherapy. Like the Lilliputians bringing down Gulliver with hundreds of weak ligatures, it may be possible to inhibit overall flux through a cancer-causing pathway using relatively weak inhibitors rather than the powerful cellular poisons currently employed.

Incomplete inhibition should limit toxicity. An inhibitor that blocked only 50% of the activity of a protein, combined with 6 other loose inhibitors, would nevertheless block overall flux through a pathway that relied on all 7 proteins by >99% ($1/2[7] = 1/128 < 1\%$).

New drugs

New chemical entities (NCE's) can be developed if absolutely necessary—if no combination of already existing and known drugs works. But the cost and probable toxicity of NCE's should make them the last resort of any healthcare system whose goal is QI.

Nevertheless, the UK is in an ideal position for drug discovery and drug development. It could easily harness the MRC and NHS to become a "peer-reviewed virtual pharmaceutical company™." The MRC could continue to fund basic scientific programs into understanding drug mechanism, whilst the NHS could supply patients for Phase I-III testing.

Funding, the rate-limiting step, could come from financial institutions hitherto not involved in pharmaceutical research, but anxious to participate in the industry, now that Big Pharma is becoming extinct.

The research pharmaceutical industry has been undergoing massive consolidation since the late 1980s, so that only a few large pharmaceutical companies are left. Evidently, the industry can no longer support as many players as it used to. The reason for this is that managed care has been limiting the use of branded drugs since the early 1980s, such that they now occupy only 30% of the market. The use of generic drugs continues to increase every year.

The fewer the drug companies left, the larger they get. The larger they are, the more risk-averse they have become. Pfizer lost 20% of its market capitalization over the failure of its HDL-raising drug last fall. Drug companies are punished in the market-place for any failures. Their response has been to let biotech companies fail instead. As a result, Big Pharma's pipelines have dried up. A huge vacuum is opening up in the pharmaceutical industry, precisely when genomics has finally made it possible to solve diseases.

Research partnership

The MRC and NHS could perform the preclinical and clinical work necessary for new drug discovery. Routine pre-clinical assays, such as absorption/detoxification/metabolism/excretion/toxicity (ADMETox), could be subcontracted to companies specializing in this work, as could chemical manufacturing. A company like GenoMed could easily supply the drug targets.

In return for its participation, the NHS could retain partial ownership of any intellectual property it helped to develop, especially new drugs. They would provide an ongoing revenue stream for the NHS during their patent life.

It light of the above discussion, I would like to try to answer the specific questions below.

Policy Framework

Who is in charge of setting and reviewing policy in this area?

In the US, the NIH and FDA.

Who provides scientific advice on policy development?

In the US, the NIH and White House Office of Science Technology and Policy. Congress is not terribly involved. The House of Lords Science and Technology Committee is to be commended for its involvement in genomic medicine.

Who monitors and anticipates potential scientific developments and their relevance to future policy?

In the US, it appears to be the NIH and HHS. The NIH just asked for outside guidance on genomic medicine, but it is pretty clear what they want to hear. The MRC would be just as closed-minded. Again, the House of Lords Science and Technology Committee is to be commended for taking up the topic themselves.

How effective are these mechanisms?

Not at all. Healthcare has remained stagnant for the past 28 years that I've been a practicing physician. Thiazide diuretics are still the first line treatment for hypertension. Just as in the 1920s, glucose control remains the mainstay of treatment for diabetes, yet complications arise at the same rates as 30 years ago.

Does the existing regulatory and advisory framework provide for optimal development and translation of new technologies?

Not at all. It takes 17 years for a new treatment to make its way into the clinic. I have personal experience that a new treatment doesn't even get reported for going on 6

years now (1). Penicillin at least made the news soon after discovery, even if it wasn't widely available for a decade. In this case, the drugs are already available, but nobody has breathed a word about the "recipe" for preventing end-stage renal disease. Healthcare has become, for all intents and purposes, anti-innovative at its core.

Are there any regulatory gaps?

Not particularly. What's interesting is that not all tumor-expression data is useful: estrogen receptor status of breast cancers makes a big difference on treatment and prognosis, but not so EGFr status of breast and lung cancers, etc. Nevertheless, anti-EGFr treatments, although horribly expensive, are prescribed and paid for. If anything, the system is too lenient about paying for expensive medication which does little to improve clinical outcomes.

In what way is science and clinical policy decision-making informed by social, ethical and legal considerations?

They need to be informed by clinical considerations above all. Ethical, legal and social implications (ELSI) have, if anything, strangled genomic research in the US. Having to get informed consent for stored samples, when the patients may have already died, seems quite unnecessary. Who could possibly be hurt by using the tissue? Such misplaced solicitude has set the field back by several decades. Our duty is to patients with the disease now who need to be helped.

How does the framework compare internationally?

Internationally, the field of genomic medicine is in its infancy. No healthcare system has a meaningful QI program in place. Clinical outcomes are still not even reported, so how can they be improved? Samples are being stored in BioBanks, but there is no funding for any but a handful of labs to access them.

Research and Scientific Development

What is the state of the science?

A "master" disease gene has been found (2) but not applied to the population yet. Its application alone should save 5% of healthcare costs within the first 12 months, and perhaps 30% over 10 years (2).

Genes for 6 cancers in whites have been found, proving that GenoMed knows how to find causative genes for all cancers and perhaps all polygenic, common diseases. In theory, we could do this for any ethnic group, not just Caucasians, although we'd need to replicate dbSNP in each ethnic group.

What new developments are there?

Linkage disequilibrium approaches, which worked well for single-gene, so-called Mendelian disorders, have not worked at all well for polygenic diseases. A recent NEJM article, for example, found a single TGF-beta dependent gene after scanning cardiovascular disease patients for 600,000 SNPs (12). An association strategy using functional rather than neutral, "marker" SNPs is far better suited to polygenic diseases.

We have evidence that (a) there are some 10,000 participating genes per polygenic disease; (b) each gene may have more than one SNP involved; (c)

consequently, the signal from any one SNP is vanishingly small. In fact, there is no linkage disequilibrium between two SNPs only 17 bases apart. One SNP, at -789 in the ecNOS promoter, has a strong [p<10(-21)] association with Disease A (NIDDM, but not diabetic nephropathy), whereas another SNP at -772 has a similarly strong [p<10(-23)] association with Disease B (diabetic nephropathy) but not Disease A (NIDDM).

Finding disease-causing polymorphisms in a sea of 3 billion letters is like fishing for cod in the Atlantic Ocean. It helps to know where the fish like to congregate. Putting down nets every 10 meters across the Ocean is a very expensive and inefficient approach. Not surprisingly, whole genome association studies have yielded little for the past two decades. Yet the pediatric geneticists and genetic statisticians who succeeded at solving single gene diseases remain in control of the funding and the overall scientific strategy for adult, polygenic diseases.

What is the rate of change?

Little new since the CF gene was discovered 25 yrs ago. Affymetrix is putting out a 1 M SNP chip, since earlier versions haven't worked. Ultimately, a 3 M SNP chip will be required, since that's the minimum number of SNPs in the Caucasian human genome. There is a much more efficient way to find disease-associated SNPs!

Who is taking the lead in the consideration and co-ordination of research and the development of new technologies?

New technology is not necessary. Existing technology is adequate, if only there were adequate funding. Waiting for new technology would be like Isabella calling off Columbus until somebody discovered the diesel engine.

How effective is the policy and investment framework in supporting research in this area?

Rather ineffective. The same expensive approach to polygenic diseases that has failed for the past 25 years continues to be funded by both the governments of the UK and the US. Big Pharma has followed suit, compounding the loss of money and time. The field is considered to be too complicated for any other approach to work. If the experts all say that linkage disequilibrium is the only way to proceed, why should a private investor believe otherwise? How could a small start-up company possibly be right when the best and the brightest names in science are unanimous in pursuing the same, albeit unsuccessful, approach?

As a result, the field is in serious danger of going nowhere. When will government finally contemplate an alternative approach? Only after the 3 M SNP chip fails? Only after the 6 M SNP chip fails?

The biggest danger right now is that we'll languish in the current state of clinical ignorance for another 50 years for lack of investment.

How does research in the UK compare internationally?

No better or worse than anybody else. Many countries are collecting BioBanks—Iceland, for the sole benefit of DeCODE; Estonia, etc. What nobody has yet done is actually solve any diseases. Or, if they're solved (1), there has been no interest in applying the solution (9).

How much collaboration is there?

None as yet.

What are the current research priorities?

In oncology, the NIH plans to use the $300K sequencing machines left over from the genome sequencing effort to sequence individual tumor genomes—the equivalent of trying to inhibit the formation of snow by carefully photographing individual snowflakes.

What is the role of industry?

Industry is currently the public's only hope—not Big Pharma, but small biotech companies like GenoMed. Pediatric geneticists and genetic statisticians are unfortunately in control of government funding, meaning that government is currently completely out of the competition. The only problem is that there is absolutely no funding for small biotech companies to carry the day.

How much cross-sector collaboration takes place?

Very little at present. Nil. There is intense disdain and distrust of industry by academia. On the other hand, academia has valuable—but replaceable—resources which could help industry. The good (and bad) news is that cancer patients can be found anywhere. Prestige matters very little. If the UK doesn't embrace the plan I propose, they will become irrelevant bystanders. Any healthcare system in the world can carry out this plan, and partners in drug discovery and development can be found in many countries, including India, China, etc. The pieces of a "virtual" pharmaceutical company are easy to assemble. The technology is already available. Funding has become the rate-limiting step.

Data Use and Interpretation

Is genomic information published, annotated and presented in a useful way?

For most diseases, it doesn't yet exist.

Should there be a common, public database?

Most of the $5-8 B a year pursuing disease-causing genomic polymorphisms would say no—that's what they're trying to discover. It would be like nationalizing the gold mines while the Forty-Niners were still flocking to California.

If so, who should fund, and have responsibility for, such an initiative?

The database will direct all of medicine for the next century at least. It will form the basis of molecular diagnostics as well as the pharmaceutical industry. For the government to run this program would require an extraordinary investment of funds and patience. Truly, it would be the "cathedral project" of the current century. But it would require a substantial change in direction. That's unlikely without a test first. A competition to achieve pre-defined milestones over a short, say 2 year period, could be arranged, for example, identification of at least 10 disease-causing genes. Winners would be allowed to proceed; the losers would not.

Who should provide the framework for optimal evaluation of data and translational opportunities?

The data is easy to evaluate according to current scientific guidelines. There is a grave danger in making any one entity the Data Tsar, since in the history of science the Data Tsar usually turns out to be wrong. What is the sensitivity and the specificity of the test? Does the diagnostic chip actually lower mortality in a prospective study? Can the results be replicated by other groups? These are standard questions which can be published in any number of already existing journals.

What policy and funding mechanisms are in place for recognising and utilising potential opportunities?

Both in the US (NIH) and the UK (MRC), there is currently no policy for funding anything but me-too science. Nor is there any meaningful funding for clinical research. Genomic medicine creates hundreds of clinical hypotheses which all beg to be tested in actual patients.

Unfortunately, the NIH and MRC have left clinical trials to research pharmaceutical companies, beginning in the 1960s. Since the 1980s, generic drugs have captured more and more of the pharmaceutical market. Currently, 70% of the drugs purchased by healthcare plans are generic. As a result, the market for branded drugs is shrinking, and research pharmaceutical companies are going out of business. A massive consolidation has been underway in the research pharmaceutical market since the late 1980s. There have been virtually no Phase IV trials since the early 1990s.

This would be an ideal time to establish a clinically oriented funding mechanism. It should be part of the NHS itself, rather than the MRC. It should consist of the following components:

1. Reporting outcomes as they currently are.

Outcomes can't be improved if we don't know where we're starting from. How well do diabetics do in Mr. X's practice? How many go on dialysis? How long before dialysis? How many have heart attacks? How many lose their limbs? How many go blind?

The next level of inquiry will be comparative. Why do the diabetics in Mr Y's practice do better than Mr X's? Is there anything Ms Y does differently than Mr X? Can we all learn something from Ms Y, or will her hard-won insight be lost to the ages?

2. Pharmacoepidemiology.

Medical genomics raises a huge number of clinical hypotheses. For example, genomic epidemiology suggests that ACE inhibitors and ARBs may be useful for at least 150 common diseases. Review of patients' prescriptions can quickly contribute information. Do patients taking an ACE inhibitor or ARB also take, for example, more or less tamoxifen than you'd expect for breast cancer? Tysabri for multiple sclerosis? Characteristic drug X for disease Y? If the odds ratio of taking an ACEI/ARB and characteristic drug X is above 1, then ACEI/ARBs lead to that disease. If the odds ratio is

less than 1, then ACEI/ARBs protect against that disease, in keeping with the genomic epidemiologic data. Prospective trials in actual patients with disease Y are next in order.

3. Molecular diagnostics.
(see discussion above)

4. Phase IV trials of existing medications, including "cocktails."
(see discussion above)

5. New drug discovery and development.
(see discussion above).

Is other medical information recorded in a suitable format to allow optimal interpretation of genomic data?

If it's on paper, it's good enough. Obviously, electronic medical records would make it easier than having to pull charts. But there's no point spending valuable time and money on developing electronic medical records. Use the money and time to find disease-causing genes and test new treatments instead.

Medicine has a long tradition of unnecessary make-work, such as the attempt at perfect blood glucose control in diabetics. Just because something can be done doesn't mean that it should be done. Only if it drastically improves clinical outcomes should patients and physicians bother.

How should genomic data be brought together with other health information?

Genomic data should simply be part of the medical chart, like other health information. In principle, genomic data is no different from any other test result.

What are the implications of the generation and storage of genome data on personal data security and privacy, and on its potential use or abuse in employment and insurance? How should these be addressed?

Anti-discrimination laws in the US (the Americans with Disabilities Act) and the UK already prevent discriminating on the basis of a person's genetic make-up. Health insurance in the UK doesn't discriminate at all, since the NHS accepts all comers, regardless of pre-existing conditions.

Genomic data will actually make it easier to achieve better clinical outcomes. Insurance companies will become more profitable by using it. They would be silly to ignore it or, worse still, punish consumers because of it.

Translation

What opportunities are there for diagnostics, therapeutics and prognostics - now and in the future?

Tremendous opportunities for all three (please see above).

Who is responsible for translation to clinical practice?

At the moment, industry, since a business case can be made for improving patient outcomes and saving healthcare costs. And government has distanced itself from clinically relevant research since the 1960s.

Given the pace of technological advance, how 'future-proof' is healthcare investment in this area?

Finding disease-associated genomic polymorphisms is completely ‘future-proof’—they need only be found once in a species’ lifetime. They will not change. In other words, getting the answer right is worthwhile; the technology for getting the answer is irrelevant.

How does the UK compare to other countries and what lessons can be learnt?

At the moment, no better or worse off than anybody else. The first healthcare system that embraces a new approach will become the global leader in genomic-based medicine.

How meaningful are genetic tests which use genome variation data?

They are the best method of pre-symptomatic diagnosis.

What progress has been made in the regulation of such tests?

Nobody has them yet, so regulating them hasn’t been much of an issue. The BRCA1/2 tests were approved before it became apparent that they predict only 5% of breast cancer in white women. It had been hoped that they accounted for more sporadic cases. In general, families get their diseases in a different way than the bulk of the population, making linkage analysis even less useful for the general population.

A large, ethnically diverse healthcare system like the NHS is in a relatively unique position to work out accurate values for genomic tests for the world’s major ethnicities: their sensitivity, specificity, positive predictive value (PPV), negative predictive value, cost-effectiveness, effect on mortality, etc.

Biomarkers and Epidemiology

In what way do genome-wide association studies contribute to the identification of biomarkers?

Surprisingly little. See, e.g., the recent largely negative search for cardiovascular disease-causing genes using 600K SNPs published in the NEJM. A single TGF-beta dependent gene was unequivocally found (12). This was already obvious in 1992 (see 1 for ref.).

We’re told to wait for the 1 M SNP chip, just as we were told, when the 100K SNP chip failed, to wait for the 600K SNP chip. A 1 M SNP chip has marker SNPs roughly every 3,000 base pairs. Yet we have evidence that two SNPs only 17 base pairs apart are completely unlinked. Continuing to pursue the same, extraordinarily expensive approach without at least exploring other avenues is poor scientific strategy. Any scientist running his/her own laboratory would have given up on this particular line of attack long ago. It’s surprising to me that the UK, which prided itself on clever rather than brute-force experimental approaches when I was a student at Oxford in the mid-1970s, is still copying everybody else 25 years later.

How is the study of genetic factors and biomarkers integrated for translational purposes?

A healthcare system that wanted to improve clinical outcomes could easily do this. But the first step would be to try to optimize clinical outcomes. The NHS doesn't even report outcomes yet. No health system does. Reporting health outcomes would be an invaluable first step for quality improvement (QI), irrespective of genomic medicine.

What impact will genomic data have on data emerging from projects such as UK Biobank, Generation Scotland and other biobanks?

The Biobanks are not as useful as directed patient collections for specific diseases. A directed strategy would be much more efficient than exhaustive sample collection. Collecting samples does not solve the disease.

Use of genomic information in a healthcare setting

What impact will genomic information have on the classification of disease?

It will be critical as an early warning system for otherwise lethal diseases, such as cancer. It may help in the treatment of currently untreatable diseases. But it won't necessarily help much with classification—other than to show that one gene may be involved in many different diseases.

How will it affect disease aetiology and diagnostic labels?

A single gene can cause multiple diseases. Genomics may break down barriers between clinical divisions. Genomics is tending to "lump" diseases together, rather than slice diseases into ever finer categories.

How useful will genomic information be as part of individualised medical advice?

Critical for assessing cancer risk and detecting cancer while still early. Probably not very important in determining specific treatment. We've found that everybody responds to an ACE inhibitor, for example, regardless of ACE I/D genotype (1). Similarly, people without a particular SNP in gene X may still respond to an inhibitor of gene X simply because the overall disease pathway involves gene X. We still don't understand what a disease pathway looks like, whether it's common to all patients with the same clinical diagnosis, etc. We'll only know how disease pathways work once we get clinical experience trying to interrupt them. To pretend otherwise at this point would be dishonest.

What provisions are there for ensuring that the individual will be able to understand and manage genomic information, uncertainty and risk?

The general provision that any information be told in a way that a 2nd grader can understand it. Genomic medicine will be the GP's duty to explain to the patient. Those establishing new tests will need to make the test intelligible to the GP.

Should there be a regulatory code (mandatory or voluntary) covering the provision of this advice?

There's no sense regulating something that doesn't even exist yet. Plus, the people presumably doing the regulating—trained genetic counselors—studied Mendelian

genetics. Polygenic diseases have not been fully characterized yet, let alone understood. So it makes little sense to have Mendelian geneticists regulating people on material they don't understand themselves.

What are the implications of developments in genomic technologies for the training of medical specialists and other health professionals?

With luck, genomics will elevate the GP and make sub-specialists redundant.

Are there any gaps that need addressing?

Geriatrics, but genomic medicine doesn't change population demographics.

What is the assessment and planning for future needs in capacity?

If genomics can increase life expectancy by a decade, people are going to have to agree to die at home once they reach 100, rather than in hospital. That's the only way for a healthcare system to save money.

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CHAPTER 5--REPORT AND ADMINISTRATION

SEC. 2151. REPORT TO CONGRESS.

Not later than 180 days after the date of enactment of this Act, the Director of the Centers for Disease Control and Prevention, in consultation with the Assistant Secretary for Medical Readiness and Response of the Department of Homeland Security and the Director of the National Institute for Allergy and Infectious Disease of the National Institutes of Health, shall submit a report to Congress that describes alternatives to traditional vaccines and anti-viral therapeutics for viral diseases, including negative immunomodulation compounds that partially suppress a macrophage-dependent innate immune response of an individual to viral pathogens, in order to decrease morbidity and mortality from an excessive immune response.

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12. Samani NJ et al. Genomewide Association Analysis of Coronary Artery Disease. New Engl J Med 357(5):443-453, August 2, 2007.