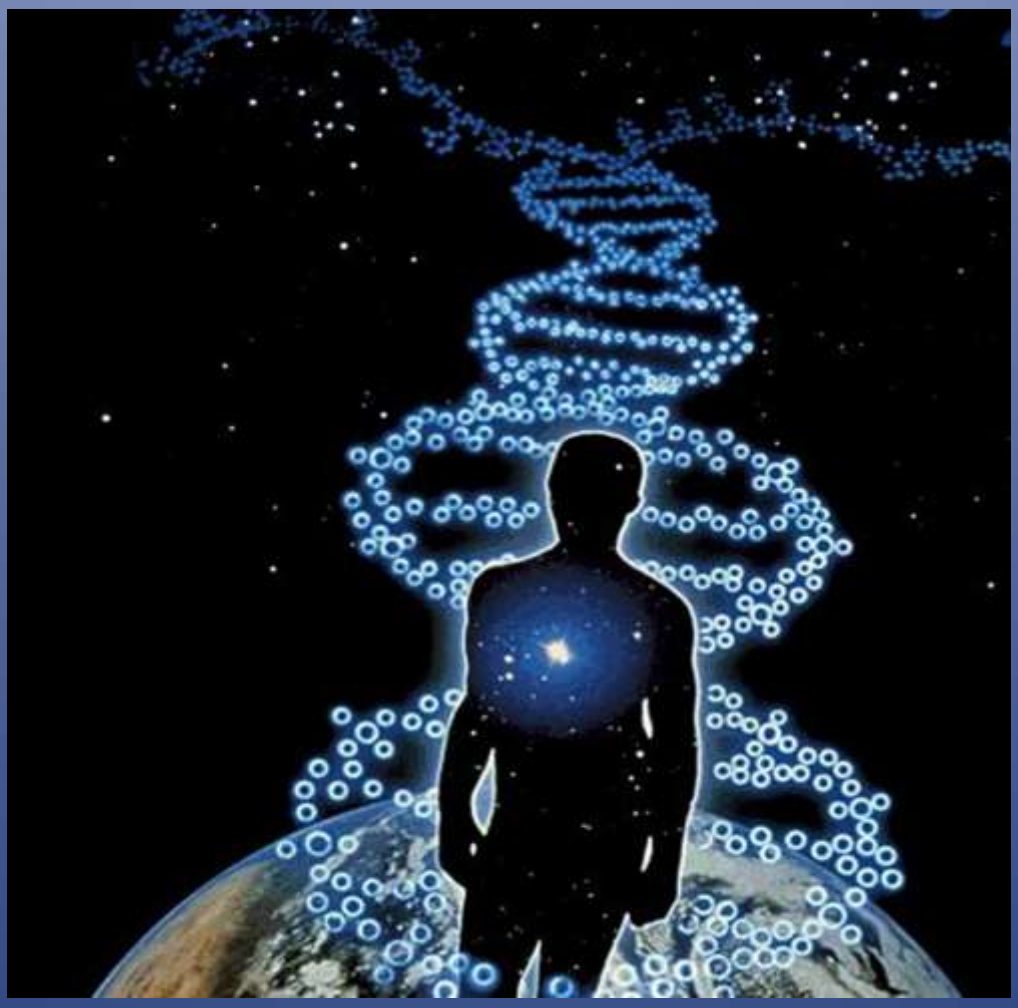
Living Longer, Living Better – DNA And Your Future



Ray Hammond (Genotype AA)

Chapter extracted from 'SCARY-WONDERFUL: THE NEXT 50 YEARS'

GETTING TO KNOW YOUR DNA

Many of the unique characteristics that make you an individual, ranging from the colour of your hair and eyes to how susceptible you are to developing certain diseases, are determined by the genetic material (long strands of DNA) you inherited from your parents.

Certain sections of DNA — known as genes — contain molecular sequences that enable proteins, the basic building blocks of life, to be assembled. However, the DNA sequences that comprise genes are not always perfect and can be prone to change. These changes, known as mutations, often lead to negligible or unnoticed traits in an organism, although some do result in significant alterations, which can be beneficial or harmful. Those altered genes that are damaging often result in death and are subsequently removed from the gene pool, while those that are deemed favourable can increase the likelihood of an organism's survival, providing a greater chance for such genes to be passed onto the next generation and help continue the success of a species.

Discovering Your Own DNA Profile

Have you had your DNA (your genes) decoded yet? If you haven't, you almost certainly will do so in the coming decade or so. If you have a child or a grandchild in the next few years it may be the new baby who becomes the first in your family to arrive fresh from the womb with his or her DNA already decoded. This will be analysed (before or after birth) so that doctors can look for genetic defects or potential health problems later in your infant's life.

How will you feel as a future parent if the hospital at which you attend pre-natal assessments offers you the chance to have your baby's DNA scanned when he or she is an embryo of just 12 weeks old? The procedure isn't dangerous or complex and the idea of prenatal therapy has been given new impetus by advances in genetic sequencing techniques; it has recently become possible to sequence a foetus's genes without risk of miscarriage, simply using foetal cells that reach the mother's blood. The test needs only a sample of saliva or blood from the father and blood from the mother

"It is very possible that whole-genome sequencing will become standard procedure for prenatal care," says Chiara Bacchelli of Great Ormond Street Hospital in London . At the moment these sorts of rare genetic disorders may be discovered only when a family's first child gets ill."[1]

A DNA scan of your growing foetus will be able to reveal if the baby belongs to the unlucky minority of infants that are born with a genetic disorder; currently 1 in 25 are born with such a condition and a quarter of all infant deaths are due to genetic defects. Imagine curing inherited conditions before they even arise. We have the gene and stem-cell therapies to do it for some conditions now – if

only we dare use them on unborn babies. The real question is, as a parent-to-be, would you really want to know your baby's future health prospects?

Recently *New Scientist* magazine commented:

> Within 10 years we can expect fetal genome sequencing to be routine, which will improve diagnosis enormously. Options for treating diseases while a child is still in the womb are also set for rapid expansion (see "Fetal healing: Curing congenital diseases in the womb").
>
> Given the option, most parents would probably prefer to know in advance if their child will be among the 1 in 25 (that are born with genetic defects). But this knowledge will not necessarily end the suffering. If fetal sequencing becomes routine, diagnosis is likely to run ahead of treatment, with many more genetic defects being detectable than can be treated.
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> To put it in perspective, a recent study found that the average person carries around 400 potentially damaging DNA variants and that 1 in 10 people is at high risk of developing a genetic disease as a consequence.

That *New Scientist* article suggests prospective parents who choose foetal sequencing will be faced with a bewildering range of diagnoses, prognoses and treatment options, often for non-life-threatening conditions or ones that will only manifest later in their child's life. The technology already allows parents (and doctors) to discover whether an unborn child has, for example, a greater than normal potential to be autistic or homosexual. How will parents (and society in general) react to such information? Will we find ourselves hankering for a simpler time when only the most serious genetic disorders were diagnosable early on?

(As if to illustrate the speed of the advances in *in-utero* treatments, as this chapter was being edited for publication news broke of a successful procedure that was carried out five years ago to a female foetus who was suffering from *Osteogenesis imperfect* [brittle bone disease].

(The mother from Taiwan found her unborn child carried the disease during ultrasound and genetic tests in the 26th week of pregnancy. The foetus' arms and thighs were broken even though she was only rolling in her mother's womb.

(Since Taiwan has not yet approved stem cell transfer within the womb, the mother went to Singapore where mesenchymal stem cells cultivated by Switzerland's Karolinska Institute were injected into a vein of the fetus at 31 weeks. Within two weeks, the foetus' broken bones were healed except for her right thigh.

(After the girl was born, she grew more slowly than normal. She underwent a second stem cell treatment in Singapore at one and a half years old. Now she is almost five and can sing, dance and run like other children and has not experienced any further bone fractures, doctors said.

(The merits of stem cell transfer within the womb is that the fetal immune system has not matured. This means it will take the transferred stem cells as its own and will not reject the second transfer.

(It is clear that medical technology and techniques are now running way ahead of regulation and ethics committees.)

Do We Want To Intervene In Human Evolution?

An even more difficult collective decision is looming: do we as a society want to intervene in human evolution? The technology for genetically repairing the germ line – the foetal cells that go on to form sperm and eggs – is in

development. That raises the prospect of being able to cure genetic diseases not just in one's own children, but in their children, and so on.

At present that is considered **ethically unacceptable**. But germ-line engineering could rid society of terrible conditions such as cystic fibrosis and muscular dystrophy. If the technology is there, surely the unethical option would be not using it? These are decisions for the future, but we need to start thinking about them now.

Of course, preventing or curing disorders in foetuses whilst they are still in the womb is nothing new. The first operation on a human foetus *in utero* took place in 1981 to fix a blocked urethra, the tube that carries urine out of the bladder. Since then the field has grown to encompass many types of surgery, such as correction of spinal cord defects to prevent spina bifida.

While foetal surgery may now be mainstream, performing stem cell therapy or gene therapy in the womb would arguably be an order of magnitude more challenging. Yet these techniques seem to represent the future of medicine, offering the chance to vanquish otherwise incurable illnesses by re-engineering the body at the cellular level. Several groups around the world are currently testing them out on animal embryos in the womb.

Meanwhile, the price of full adult genome sequencing is falling rapidly – it has fallen 100,000 fold in the last ten years.

"We're heading for £100 a (full) genome and that will happen in the very near future," said Sir John Bell, professor of medicine at Oxford University and a senior UK government adviser on medical genetics, speaking recently[2].

Now, the Chinese have arrived in the DNA decoding business: MIT Technology review ran the following story under the headline: Inside China's Genome Factory:

> Sequencing a complete human genome may soon cost less than an iPhone. Will BGI-Shenzhen decode yours?
>
> …in a retrofitted shoe factory that is the headquarters of BGI-Shenzhen, the 21-year-old is orchestrating an effort to decipher the genetic makeup of some 2,000 people—more than 12 trillion DNA bases in all.
>
> BGI-Shenzhen, once known as the Beijing Genomics Institute, has burst from relative obscurity to become the world's most prolific sequencer of human, plant, and animal DNA. In 2010, with the aid of a $1.58 billion line of credit from China Development Bank, BGI purchased 128 state-of-the-art DNA sequencing machines for about $500,000 apiece. It now owns 156 sequencers from several manufacturers and accounts for some 10 to 20 percent of all DNA data produced globally. So far, it claims to have completely sequenced some 50,000 human genomes—far more than any other group.

Why I Decided To Have My Own DNA Variations Decoded

Not every healthy human adult will want to have his or her own DNA decoded. When I ask my audiences how many of them think they might like to have their own DNA decoded, the split almost usually comes down to about fifty-fifty. Half the people I meet around the world think they might like to know about health implications of their own genetic code, the other half would prefer not to know (at least not at present, given today's general low level of understanding of the importance of DNA information and the widely different interpretations).

My own reasons for having key parts of my genome variations decoded were two-fold; firstly I wanted to understand the process for reasons of my own research as a futurist and, secondly, I was an adopted child and I have no

medical history for either my biological mother or father. Most readers will have an indication of their genetic inheritance by looking at the medical histories of their parents. In fact, for many common illnesses of developed countries, the strongest predictor of risk is family history. When this is missing, decoding genes becomes more important, and so it was (and is) for me.

It is important to stress that *very little is definite* when it comes to understanding the implications of an individual DNA profile and interpretations can vary. The human genome was first decoded in 2000 and, initially, it was thought that our understanding and reading of human genes would lead very quickly to revolutionary cures and treatments for some of the worst human diseases and conditions. This hasn't happened and the reason is that we quickly discovered that chromosomes and the genes they contain interact in far more subtle ways than we first imagined and whilst one set of genes, or an individual gene or an allele (one of two or more forms of a gene or a genetic locus) may indicate propensity to a particular disease (or an individual resilience), another set of genes, or a gene or an allele may contradict and counteract that propensity.

In 2010, The New York Times ran a story headlined "A Decade Later, Genetic Map Yields Few New Cures".

> Ten years after President Bill Clinton announced that the first draft of the human genome was complete, medicine has yet to see any large part of the promised benefits.
>
> For biologists, the genome has yielded one insightful surprise after another. But the primary goal of the $3 billion Human Genome Project — to ferret out the genetic roots of common diseases like cancer and Alzheimer's and then generate treatments — remains largely elusive. Indeed, after 10 years of effort, geneticists are almost back to square one in knowing where to look for the roots of common disease.

We should not really have been surprised at the level of complexity that was revealed in the newly unravelled human genome. In a prescient 2001 paper "Implications of the Human Genome Project for Medical Science" written by Doctors Francis S. Collins and Victor A. McKusick soon after the human genome was first decoded, the authors warned:

> Information about the human genome sequence and its variants must be applied to identify the particular genes that play a significant role in the hereditary contribution to common disease. This will be a daunting challenge. For a disease such as diabetes mellitus, 5 to 10 (or maybe more) genes are involved, each of which harbors a variant conferring a modest degree of increased risk. Those variants interact with each other and the environment in complex ways, rendering their identification orders of magnitude more difficult than for single gene defects. Nonetheless, with the combination of careful phenotyping (so that different disorders are not inadvertently lumped together) and sampling genetic variants at high density across the genome, it should be possible to identify disease gene associations for many common illnesses in the next 5 to 7 years. One should not underestimate, however, the degree of sophistication in clinical investigation that will be necessary or the need for development of more efficient genotyping technology, such as the use of DNA chips or mass spectrometry, to make this kind of genome-wide survey a reality.
>
> An understanding of the major pathways involved in normal homeostasis of the human organism must be developed along with how those pathways are deranged in illness. Identification of each gene that harbors a high-risk variant will point toward a critical pathway for that illness. Many of those will come as a surprise, since the current molecular understanding of most common diseases is rather limited.

In other words, the whole DNA thing is far more complex than we first imagined. But now, well over a decade after the human genome was first decoded, we are finally beginning to make some progress. As The Wall Street Journal commented in 2012:

> A decade ago, the completion of the Human Genome Project sparked optimism that cures for debilitating diseases were just around the corner. Cures still generally elude us, but now the ability to map human DNA cheaply and quickly is yielding a torrent of data about the genetic drivers of disease—and a steady stream of patients who are benefiting from the knowledge. On other fronts, technology is

> putting more power in the hands of patients, and researchers are learning to combat disorders by harnessing the body's own ability to heal and grow.

What I Learned From My DNA

So, what did I learn after the key tiny variations of my DNA – my SNPs (single-nucleotide polymorphisms, pronounced "Snips") – had been decoded by a California-based company called 23andme[i] and the results posted online for me to view on a password-protected web site?[ii]

Well, to start with one trivial (but still useful) result, it turns out that I am resistant to the common form of Norovirus – also known as the "winter vomiting bug". This means that if I were on a cruise ship and the Norovirus bug struck down passengers I could volunteer to work in the ship's hospital as I would be unlikely to catch that virus myself.

This is how 23andme describes my genetic resistance:

> The "stomach flu" isn't really the flu at all. It's actually "viral gastroenteritis," and its most common cause is a group of viruses collectively called noroviruses. No matter what you call it, the illness is highly contagious and very unpleasant — symptoms include abdominal pain, vomiting, and diarrhea. In close quarters, an outbreak can quickly spread from person to person, earning the sickness the nickname "cruise ship disease." A lucky few, however, are resistant to the most common strain of norovirus because of their genetics.
>
> Result:
>
Who:	Ray Hammond
Genotype:	AA
What it means:	Resistant to infection by the most common strain of norovirus

> Genes vs. Environment

[i] So named because there are 23 pairs of human chromosomes

[ii] Sales of direct-to-consumer genetic testing is restricted in some countries; e.g. in France, and in a few U.S. states, including New York and Maryland (and at the time of writing the FDA is threatening 23andme with a ban across the whole United States).

> Norovirus resistance is highly heritable. If you have two copies of the A version of this SNP, you lack a functioning FUT2 gene and are most likely resistant to the virus. Genetic changes other than the SNP 23andMe reports may allow people to be resistant even if they do not have the AA genotype.

I also discovered that if I am unlucky enough to have a stroke or a heart condition in the future one of the most commonly described drugs for thinning the blood and reducing damaging clots – a drug known generically as Clopidogrel – will have a reduced protective effect on me. 23andme says:

> Clopidogrel doesn't inhibit clotting to the same extent in everyone. For some people, genetic variations that prevent the drug from being converted into its active form in the body are the cause. Studies have shown that people who are taking clopidogrel who have these genetic variations may have reduced protection from heart attacks, strokes and death from cardiovascular causes.

I have a genetic make-up which means that I would not benefit as much as most people if I were given this drug. I've also learned that I am more likely to suffer vomiting after a general anaesthetic and if I were unlucky enough to contract MS (muscular dystrophy) in the future I would respond far better than most people to the most commonly described drug treatment – Interferon.

Altogether 23andme has so far provided me with 22 reports on how I would be likely to interact with widely prescribed drugs.

I also have information about 26 diseases for which I have an "elevated risk" of contracting. At the top of this list is Type II Diabetes (my risk is 36.3%, the typical risk in the population is 25.7%), followed by Colorectal Cancer (6.7% - 5.6%) and then by Ulcerative Colitis (1.3% - 0.8%).

I am then provided with a list of 31 diseases of which I have a reduced risk of contracting. Top of the list is prostate cancer (my risk is10.1% – typical risk in

the male population is 17.8%), Psoriasis (7.1% - 11.4%) and Alzheimer's disease (4.9% - 7.2%).

Then (at the time of writing) I am presented with a list of 64 diseases of which I have "typical odds" of contracting. (23andme periodically adds new results as new studies become available.)

(It is important to stress again that these figures are *merely indicative* – my lower percentage chance of suffering from Alzheimer's disease doesn't mean I won't get it, just as my higher odds of contracting Type II Diabetes doesn't mean I will develop that condition. Genetic results must be interpreted with extreme care. Often this is best done by a medical professional.)

STOP PRESS: As I was preparing this chapter for publication the U.S. Food And Drug Administration (FDA) issued a letter to 23andme ordering the company to temporarily stop selling its DNA testing kits. The FDA accuses the company of failing to provide evidence about the veracity of its testing procedures for the medical forecasts it makes. These forecasts are based upon a customer's decoded DNA (even though 23andme only points to scientific studies and reports that suggest the involvement of DNA elements, rather than asserting correlation itself). The FDA initially gave 23andme 15 days to provide the evidence or risk regulatory investigation. (As you read this the row will still be on-going – see appendix for a wide range of comments).

The nub of the FDA's complaint seems to be that 23andme hasn't itself independently proven the veracity of its DNA testing procedures (even though the Illumina computer processors which do the sequencing have been approved by the FDA themselves and are happily in use in thousands of labs and hospitals around the world) and that 23andme is providing medical diagnostic

information that only a physician should provide (which suggests the FDA may have the interests of the traditional medical profession at heart, indeed the FDA's warning to 23andme "hints strongly that some tests may be banned even if they are as accurate as the tests you could receive through a physician").

(See here for a doctor's view on why consumers are insufficiently educated to be trusted with their own DNA information and its possible implications.)

The FDA suggests, for example, that a woman who receives 23andme results which indicate that she is at high risk of contracting breast cancer might rush into an ill-advised double mastectomy based solely on 23andme's results. (This example of 23andme's DNA results having the potential to do consumers harm blithely ignores the fact that, at the very least, a surgeon would have to be involved to help the woman procure the procedure.

Many commentators are accusing the FDA of heavy handedness, some are suggesting that the FDA is approaching 21st Century genomics with outdated 20th Century regulatory tools and some are suggesting the agency is protecting entrenched interests in the healthcare industry. As medicine in the USA is so heavily commercialised (compared to most other developed nations) there may be some truth to some of these accusations. As FastCompany makes clear under a headline "Why 23andme terrifies medical insurance companies":

> "What these health insurance executives make clear is they are a business, and if consumers of their business have DNA information that they [themselves] do not have in order to practice their underwriting, they cannot function," Dr. Robert Green, a medical geneticist and genomics researcher at Harvard Medical School told *Fast Company*. Insurance, after all, is economics, and economics doesn't do well with uncertainties.

Whatever the rights and wrongs of the individual 23andme case, today there are some early practical uses of gene mapping, for example:

–A personalized blood test can tell whether a patient's cancer has spread or come back. Dr. Bert Vogelstein of Johns Hopkins University in Baltimore and colleagues found stretches of DNA in colon and breast tumours with extra DNA copies, or fused-together chromosomes[iii].

–A gene-based test called Oncotype DX made by Genomic Health Inc. helps identify breast cancer patients who are not likely to benefit at all from chemotherapy.

– Dr. James Lupski of the Baylor College of Medicine in Houston studied his own entire DNA map and sequenced the genomes of family members – including his deceased grandfather – to diagnose the mutation causing his rare genetic nerve disease, called Charcot-Marie-Tooth syndrome.

So, How Much Help Is DNA Information In My Own Health Care?

I have a middle-aged family doctor who wrote a paper in the mid-1990s for other doctors advising them how best to handle patients who were then beginning to arrive at surgeries with print-outs from the internet under their arms, certain from their on-line research that they had developed sudden and life-threatening conditions.

So, more than a decade later, I went to visit my doctor armed with my new DNA variation results "under my arm" and, after describing me as "his worst

[iii] The FDA now lists 118 approved drugs that include information about pharmacogenomic markers in their labels..

nightmare", he laughed and eagerly looked at my results that were posted on-line. Then he threw up his hands and admitted that Britain's National Health Service has no policy regarding use of DNA information and no methods for making use of such information.

But that was in 2009 and since that time the UK has turned into a world leader in advancing the cause of gene-based medicine.

In 2010 a massive non-for-profit DNA-gathering project called "The UK Biobank" completed the collection of blood, urine and saliva samples for future DNA analysis from 500,000 British residents between the ages of 40 and 69 (volunteers old enough to contract diseases or health conditions sooner rather than later).

All volunteers consented to have their DNA sequenced and their health tracked, anonymously, through the British National Health Service. At the time the samples were taken, data were collected including information on a participant's health and lifestyle, hearing and cognitive function, all collected through a touchscreen questionnaire and brief verbal interview. A range of physical measurements were also performed, and which included: blood pressure; arterial stiffness; eye measures (visual acuity, refractometry, intraocular pressure, optical coherence tomography); body composition measures (including impedance); hand-grip strength; ultrasound bone densitometry; spirometry; and an exercise/fitness test with ECG.

In the future this biobank will be of immense value in identifying the role of DNA types in disease development and other conditions (as the volunteers age and contract illnesses, etc.) and, because other data was also collected (lifestyle,

medical history, etc.) real understanding of the genes-lifestyle interaction is likely to emerge.

And Cancer Research UK is currently conducting trials that could lead to a simple blood test than can detect breast cancers in their earliest stage. During the trials – which are being conducted at London's Charing Cross Hospital – researchers will take blood samples from women attending the breast screening clinic and compare the DNA in the blood of women who are diagnosed with breast cancer with those that do not have cancer to see what DNA markers are consistent and which are not.

Then, in early December 2012 the UK government announced:

> **New proposals to introduce high-tech DNA mapping for cancer patients and those with rare diseases, within the NHS in England.**
>
> The UK will be the first country in the world to introduce the technology within a mainstream health system, with up to 100,000 patients over three to five years having their whole genome – their personal DNA code – sequenced.
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> The genome profile will give doctors a new, advanced understanding of a patient's genetic make-up, condition and treatment needs, ensuring they have access to the right drugs and personalised care far quicker than ever before.
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> It will also help to develop life-saving new drugs, treatments and scientific breakthroughs, which experts predict could significantly reduce the number of premature deaths from cancer within a generation.

A budget of £100 million was announced for this initiative – and, rightly, it will be primarily focussed on cancer sufferers (cancer is largely a disease caused by changes of DNA sequence). But today, even before the cancer patient DNA mapping programme has started, the British NHS could be saving millions of pounds each year if it simply knew which of its patients was receptive to certain

drugs and resistant to others. The cost-benefit case for at least mapping variations in patients' genes (their SNPs) is overwhelming.

In the USA at the Beth Israel Deaconess Medical Center just such a cost-benefit analysis of DNA- prescription targeting is being carried out:

> Ramy Arnaout, MD, DPhil, a founding member of the Genomic Medicine Initiative at Beth Israel Deaconess Medical Center (BIDMC), who is using cost-benefit analysis and quantitative modelling to analyze which drug prescriptions can be better matched to a person's genome. Arnaout and his team published the results of their analysis in a recent issue of *Clinical Chemistry*.
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> There is lots of money at stake—it's estimated that drug-related adverse outcomes cost the health-care system upwards of $80 billion a year. Arnaout is convinced that applying "Monte Carlo modeling" to choosing and dosing drug prescriptions according to a person's genome could save billions of dollars each year.
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> The blood-thinning drug warfarin is a prime example. In some cases, patients' genomes contain variants that make the standard dose of warfarin too high for them and those individuals are likely to experience bleeding, an extremely dangerous side effect. According to Arnaout, three-quarters of the variability in warfarin dosing requirement is due to genomic variants. Scientists have already identified a set of variants in six specific genes that explain two-thirds of the variability.
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> A lot of work remains to be done. The BIDMC team has developed a model to estimate how much it would cost to further develop and implement a pharmacogenomics system to cut these adverse outcomes in half. While considerable, it is a drop in the bucket relative to the savings; they estimate the cost at less than $10 billion spread out over approximately 20 years.

And it is becoming more possible to identify more than 80 genes which may lead to prostate, ovarian and breast cancers. The following appeared recently in The Independent newspaper:

> Men could be routinely screened for prostate cancer by GPs within five years using a simple saliva test to detect the smallest genetic mutations that collectively increase the risk of developing the potentially fatal illness, scientists said today.

> Advances in detecting the many dozens of DNA mutations linked with a range of cancers, including ovarian and breast cancers, will lead to a revolution in the early diagnosis and treatment of tumours that would otherwise go undetected, they said.
>
> The latest results of a pan-European study comparing the genomes of 100,000 patients with prostate, ovarian and breast cancers with the DNA of 100,000 healthy individuals has discovered more than 80 additional regions of the human genome linked with these cancers.

Educating The Medical Profession And The Public About The Benefits Of DNA Mapping

However, before gene variation mapping (SNP mapping, technically known as Exome sequencing) goes mainstream there are practical and cultural issues to be considered. Scientific American warned in 2012:

> To achieve a broader embrace of the $1000 genome, the public itself will need more education on the mechanics and benefits of personalized medicine. Limited or incorrect information can cause dangerous misunderstandings and illogical fear or bias against the technology amongst the public, and poor interpretation of the results by amateur geneticists might have serious negative side effects on health. Governments will have to incorporate into the current medical system ways to educate both health practitioners and patients with knowledge on how to interpret the results and be sure that they act appropriately upon them.

And, discussing the value and problems associated with consumer genetics, a feature writer for MIT Technology Review commented:

> For now, the biggest problem with consumer-friendly genetic products is simply that they may be medically inconclusive for most people. Indeed, I was more interested in the result that my genome was 2.7 percent Neanderthal (a tad higher than the 2.6 percent average for people of northern European descent). But as the costs of medical care continue to skyrocket and many individuals look for more opportunities to control their own health, these tests—if they become more powerful—could become an essential tool for understanding our bodies and helping guide us to behaviors and choices that will lead to better outcomes.

> What will keep me returning to this technology will be the updates sure to come from the scientific community as researchers continue to decipher the medical meaning of the human genome. Of the million DNA variants that 23andMe examines, fewer than 1,000 are part of the health report. The rest wait for evidence linking them to traits. In some ways the story of consumer genetics parallels that of human genomics as a whole: the challenge ahead is to figure out what specific genetic variations signify and then study them in a health context to see whether they make a real difference to patients and doctors. It would be a shame to restrict personal genetic tests now, before they have a chance to become more useful. Rather, consumers should be allowed to explore their genetic makeup to help figure out how the information can be used to make smarter medical decisions.

Examples Of Valuable DNA Mapping

Illustrating the vital value of DNA information in cancer treatment, the heart-warming story below appeared in The Wall Street Journal at the end of 2012:

> One answer (to finding new cancer treatments) is a test developed by Foundation Medicine Inc., a Cambridge, Mass., startup whose scientific founders include one of the leaders of the Human Genome Project. The test, officially launched last June (2012), enables doctors to test a tumor sample for 280 different genetic mutations suspected of driving tumor growth.
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> This changes "everything in terms of how we approach patients with cancer," says David Spigel, director of lung-cancer research at the Sarah Cannon Research Institute in Nashville, Tenn. He used the test in one patient with advanced disease and few apparent options. She turned out positive for an alteration in a gene targeted by several drugs currently in development. She was signed up for one of the studies. A short time later, "she's like a new person," he says. "She's off pain medicines. She gained her weight back."
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> Michael Pellini, Foundation's chief executive officer, says that more than 600 oncologists have requested the test, which lists for $5,800. So far, he says, about 70% of cases have turned up a mutation that is potentially targeted by a drug on the market or in a clinical trial.
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> In one recent case, Dr. Pellini says, a sample from a woman with advanced pancreatic cancer yielded a response for "her2," an alteration associated with a certain form of breast cancer. She was treated and her cancer responded to the breast-cancer drug Herceptin. Few oncologists would think to look for her2 in a patient with pancreatic cancer, he says.

Despite this anecdotal evidence (and some positive results in clinical trials) most national health organisations are ultra-conservative and they are slow to implement the potential of DNA mapping in general healthcare. In 2010 the White House put out the following statement:

> With federal officials pursuing the goal of a personal human genome map under $1,000 in five years (White House, 2010), it is possible to envision a future where treatments are tailored to individuals' genetic structures, prescriptions are analyzed in advance for likely effectiveness, and researchers study clinical data in real-time to learn what works. Implementation of these regimens creates a situation where treatments are better targeted, health systems save money by identifying therapies not likely to be effective for particular people, and researchers have a better understanding of comparative effectiveness (President's Council of Advisors on Science and Technology, 2010).

But a couple of years later a writer for the Bookings Institute commented on progress in the field that in the USA is known as "Personalized Medicine"[iv]:

> Yet despite these benefits (of DNA mapping), consumer and system-wide gains remain limited by an outmoded policy regime. Federal regulations were developed years before recent advances in gene sequencing, electronic health records, and information technology. With scientific innovation running far ahead of public policy, physicians, researchers, and patients are not receiving the full advantage of latest developments. Current policies should leverage new advances in genomics and personalized medicine in order to individualize diagnosis and treatment. Similarly, policies creating incentives for the adoption of health information technology should ensure that the invested infrastructure is one that supports new-care paradigms as opposed to automating yesterday's health care practices.

But despite foot-dragging by some members of the medical community Personalized Medicine[v] is looming on the horizon (the opposite phrase

[iv] See a definition of "Personalized Medicine" at http://healthworkscollective.com/eileen-obrien/75796/what-personalized-medicine

"Impersonal Medicine" accurately describes current healthcare approaches). Under a headline "Personalized Medicine Moves Closer", The Wall Street Journal reported late in 2012:

> In a major step toward an era of personalized medicine, researchers reported Wednesday that they have sequenced the complete DNA material of more than 1,000 people from 14 population groups in Europe, Africa, East Asia and the Americas.
>
> The report from the $120 million 1000 Genomes Project involved 700 scientists from laboratories in the U.S., Canada, China, Japan, Nigeria and Kenya, among others. Their results, published in Nature, offer the closest look yet at the differences in humankind's biological instruction set, documenting how myriad rare mutations may underpin many diseases and set the people of one locale apart from another in ways that shape their health.
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> "We are getting to the point where an individual genome sequence can be a useful part of diagnosis," said statistical geneticist Gilean McVean at Oxford University in England, who led the effort. "If there is a variation that is present in just one in 100 people, we have found it,"

Of course, there are potential *disadvantages* to having your genome mapped – but these disadvantages spring from our past and present policies in health-care provision, rather than from medicine itself. Until very recently U.S. citizens were scared to have any part of their DNA decoded in case health insurance was refused as a result or in case employers demanded such information[3].

But today the 2009 "Genetic Information Nondiscrimination Act (GINA)" is in force in the U.S.A and, in a limited way, it protects American citizens against discrimination based on their genetic information when it comes to health insurance and employment. Full details of the protections can be viewed here.

But GINA does not address adverse selection in life insurance for U.S. citizens, where concerns are more serious because there is no natural limit on payouts,

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[v] I think the phrase "Individualised medicine" would be a more accurate description of DNA-based healthcare in the future.

and because the product is regarded as more discretionary than health insurance itself. In any event, why should insurers be prevented from calibrating their risks in this area? After all, the government currently recognises the needs of the insurance sector to increase levels of premiums and even not to offer insurance on grounds of age in certain circumstances; why not predisposition to certain disorders, if they are as predictive as age? *Actuarial fairness and fairness before the law come fatally asunder at this point*. Neither does GINA protect U.S. citizens from discrimination in the provision of disability insurance and long-term care insurance – two vital areas where genetic information is crucial.

Citizens of other nations have even less protection than Americans. Shortly after I first received my DNA decoding I took out annual travel insurance. I travel a lot so I try to be scrupulous in providing all of the information relevant to an insurer so that the insurer has less "wiggle room" if the time ever comes that I need to make a claim. But one of the questions I was asked on the application form was: "Is there any other information about your health that would reasonably be deemed relevant to our assessment of health and other risks?"

The question is fatally open-ended and, if my DNA mapping had shown a higher than usual likelihood of me suffering a heart attack, was I legally obliged to disclose this? After all, if this were true, the information would not have come from a medical professional and it would not be included in my health records. Did I, in fact, disclose everything with potentially adverse consequences to my providers of travel insurance? I shall leave it to you to judge how I responded to that question.

In the UK People with adverse genetic test results may also be discriminated against in the future by insurers or employers. The Equality Act 2010 should

prevent employers demanding or commissioning DNA test results, but British insurers are prevented from using most genetic test results only by a voluntary agreement. This needs to be strengthened, but, because of austerity measures, the British government recently closed the Human Genetics Commission – the sole body that was reporting to parliament on ethical and moral issues connected with genetics, DNA testing, data gathering and genetic discrimination. There is no current champion for UK citizens regarding genetic rights.

Elsewhere in the world there is little specific protection for citizens whose DNA profile reveals something negative. Internationally there is a political and legal vacuum[4].

Early Success Stories Produced By DNA Mapping

Under the headline "In Treatment for Leukemia, Glimpses of the Future" the New York Times ran the following story in July 2012:

> Genetics researchers at Washington University, one of the world's leading centers for work on the human genome, were devastated. Dr. Lukas Wartman, a young, talented and beloved colleague, had the very cancer he had devoted his career to studying. He was deteriorating fast. No known treatment could save him. And no one, to their knowledge, had ever investigated the complete genetic makeup of a cancer like his.
>
> So one day last July, Dr. Timothy Ley, associate director of the university's genome institute, summoned his team. Why not throw everything we have at seeing if we can find a rogue gene spurring Dr. Wartman's cancer, adult acute lymphoblastic leukemia, he asked? "It's now or never," he recalled telling them. "We will only get one shot."
>
> Dr. Ley's team tried a type of analysis that they had never done before. They fully sequenced the genes of both his cancer cells and healthy cells for comparison, and at the same time analyzed his RNA,

> a close chemical cousin to DNA, for clues to what his genes were doing.
>
> The researchers on the project put other work aside for weeks, running one of the university's 26 sequencing machines and supercomputer around the clock. And they found a culprit — a normal gene that was in overdrive, churning out huge amounts of a protein that appeared to be spurring the cancer's growth.
>
> Even better, there was a promising new drug that might shut down the malfunctioning gene — a drug that had been tested and approved only for advanced kidney cancer. Dr. Wartman became the first person ever to take it for leukemia.
>
> And now, against all odds, his cancer is in remission and has been since last fall.

And even HIV, that most troublesome of immune system diseases may eventually yield to gene therapy. The story of a young HIV sufferer who became free of the disease after a bone-marrow transplant was reported by the Financial Times:

> Hopes of finding a cure for HIV were raised two years ago, when it was revealed that a patient being treated in Germany had been cleared of the virus after receiving a bone-marrow transplant in 2007. This raised the possibility that defeating Aids was a step closer.
>
> Known as the "Berlin patient", Timothy Brown, who had leukaemia and HIV, received the transplant from a donor who had a rare genetic mutation that made him resistant to HIV
>
> Mr Brown remains free of HIV, and his case has opened the possibility of replicating that success through gene therapy in other infected patients without the risks of bone-marrow transplants.

And "Business Week" reported on the value DNA information about a tumour can provide to cancer sufferers:

> In March 2009, Diane Carlini had a routine mammogram and got a preliminary diagnosis of breast cancer on the spot. She then underwent a gamut of tests including a painful biopsy and an MRI, followed by surgery to remove her tumor. Throughout the process, an unnerved Carlini tried to gauge the severity of her illness by reading

> the faces of doctors and parsing their less-than-precise takes on her condition. “With the mammogram, you could tell they weren’t completely sure what was going on,” she says. “And the same was true of the biopsy, where they could see some bad cells, but there was plenty of doubt.”
>
> The only real moment of clarity for Carlini, who handles public relations for the tax software maker Intuit, came about a month into the ordeal. That’s when her three-page report from Genomic Health arrived, providing a detailed analysis of the genetic makeup of her tumors and how likely they were to respond to chemotherapy and to recur. Carlini found out there was a 29 percent chance her cancer would return without chemotherapy; the chances would fall to 15 percent with chemo, which she opted to have. “Somebody finally gave me some concrete information and a real recommendation,” says Carlini, whose cancer is now in remission. “I hung on to that—that those numbers were valid—through the whole treatment process.”

It is clear than DNA analysis significantly increases the effectiveness of treatment in some cases.

The Future Of DNA Mapping and Personalised Medicine

In the excellent, previously mentioned 2001, paper “Implications Of The Human Genome Project For Medical Science” the authors suggested what DNA test might become possible by the year 2010.

> By the year 2010, it is expected that predictive genetic tests will be available for as many as a dozen common conditions, allowing individuals who wish to know this information to learn their individual susceptibilities and to take steps to reduce those risks for which interventions are or will be available. Such interventions could take the form of medical surveillance, lifestyle modifications, diet, or drug therapy. Identification of persons at highest risk for colon cancer, for example, could lead to targeted efforts to provide colonoscopic screening to those individuals, with the likelihood of preventing many premature deaths.

That prediction was spot on. Then the same authors hazarded a guess at what might be possible ten years later:

> By 2020, the impact of genetics on medicine will be even more widespread. The pharmacogenomics approach for predicting drug responsiveness will be standard practice for quite a number of

> disorders and drugs. New gene-based "designer drugs" will be introduced to the market for diabetes mellitus, hypertension, mental illness, and many other conditions. Improved diagnosis and treatment of cancer will likely be the most advanced of the clinical consequences of genetics, since a vast amount of molecular information already has been collected about the genetic basis of malignancy. By 2020, it is likely that every tumor will have a precise molecular fingerprint determined, cataloging the genes that have gone awry, and therapy will be individually targeted to that fingerprint.

I hope that prediction turns out to be equally accurate.

Gene Therapy Finally Arrives

China was the first nation to approve the use of "gene therapy" (using genes to affect, alter or replace defective genes in humans) in 2003 – and they were way ahead of all other countries, whether because of progressive attitudes by medical authorities or because of a less strict regulatory regime is unclear. As the journal Nature Biotechnology reported:

> China became the first country to approve the commercial production of a gene therapy, and it is due to hit the market in early January (2004). Despite technical hurdles and the wary attitude of regulatory authorities outside China, other countries are expected to soon follow suit.
>
> On October 16, 2003, Shenzhen SiBiono GenTech (Shenzhen, China), obtained a drug license from the State Food and Drug Administration of China (SFDA; Beijing, China) for its recombinant Ad-p53 gene therapy for head and neck squamous cell carcinoma (HNSCC)—a cancer that accounts for about 10% of the 2.5 million annual new cancer patients in China. Sold under the brand name Gendicine, the world's first commercial gene therapy uses an adenoviral vector and cost the company more than RMB 80 ($9.6) million to develop in addition to research grants they received from government.
>
> "We have had more than five years of clinical trials, and the only side effect of Gendicine is self-limited fever," says Zhaohui Peng, chairman and CEO of SiBiono. After eight weeks of a joint treatment of radiotherapy and weekly gene therapy injections, 64% of late-stage HNSCC tumors experienced complete regression and 32% experienced partial regression.

In the end it was not until 2012 (nine years later) that the European Union approved Europe's first ever gene therapy for use on the public. As The Wall Street Journal reported:

> After years of controversy, gene therapy is poised to become a viable option for a variety of often life-threatening medical conditions, especially those resulting from a single defective gene. Last month, the European Union approved Glybera for treatment of a rare genetic disease, making it the first gene-therapy medicine approved in the Western world. The approval comes amid a flurry of research showing broader promise for the approach in a range of disorders, from a rare form of blindness to hemophilia to heart failure.
>
> … Gene therapy's tantalizing attraction is that a single treatment has the potential to cure lethal diseases by enabling normal genes to take over for defective ones. The treatment involves loading a functional gene onto a fragment of a deactivated virus that transports the gene to a cell's nucleus, where it is intended to take over.

And plenty of work is now going on to develop other gene therapies. For example, Bluebird Bio, a gene-therapy startup company in Massachusetts, expects to soon launch studies for two rare genetic diseases: childhood adrenoleukodystrophy, or ALD, an inherited and lethal neurological disorder; and beta thalasemia, which causes the destruction of red blood cells and leads to life-threatening anemia. Its technique involves extracting a patient's own bone-marrow cells, isolating certain stem cells, and delivering the gene therapy before returning the cells to the body. According to Nick Leschly, Bluebird's president and chief executive officer, four boys in Paris with ALD have been successfully treated, including two first treated nearly six years ago. They are now in their teens and would otherwise likely have died before age 10, BluebirdBio claims.

In Sweden, two geneticists have genetically modified a virus to eat only tumours – a cancer of cancers. Despite being proven in clinical trials, finance is lacking for development. The Guardian reported:

> Two researchers at the University of Uppsala have engineered a virus that will attack cancer. Cheap, precise, with only mild, flu-like side-effects, this plucky little microbe sounds too good to be true. Yet in peer-reviewed articles in top journals, Professor Magnus Essand and Dr Justyna Leja have repeatedly showed that Ad5[CgA-E1A-miR122]PTD views healthy tissue with disdain; it eats only tumours. It is, in effect, a cancer of cancer.
>
> That viral infections can eliminate cancer cells has long been known. In 1896, a German woman with leukemia went into remission after catching flu. Her bloated liver and spleen shrank to almost normal size; her explosive white blood cell count dropped 70-fold. Some cancer patients who caught measles, hepatitis or glandular fever experienced temporary recovery. In 1949, in a rather wild set of experiments, patients with Hodgkin's lymphoma were injected with viral hepatitis: one died, 13 contracted hepatitis, but seven experienced temporary improvement. It wasn't until the swell in understanding of genetics in the 1990s that scientists learned how to manufacture and control the anti-tumour effect of these anti-cancer bugs.

Other current gene-therapy efforts include Novartis SA's NOVN.VX -0.43% partnership with the University of Pennsylvania on a treatment for cancer, GlaxoSmithKline's alliance with Italian scientists for a range of disorders, and Celedon Corp.'s clinical trial of a gene therapy in patients with advanced heart failure.

Several research projects are now underway in an attempt to cure or treat different forms of blindness with gene therapy. There have been notable successes in the last five years. Eyesight in patients with Leber congenital amaurosis, a rare form of blindness, has improved markedly. The youngest research subjects show the most-dramatic improvements. And although their vision is by no means perfect, some are no longer classified as legally blind.

In the initial trials, only one eye was injected, as a precaution. This year, scientists were sufficiently emboldened by the early results that they treated the remaining eye, further improving vision.

Gene therapy is today being used for an increasingly wide range of human diseases and conditions and there are indications that seemingly impossible "cures" may be imminent. Heart attack survivors often suffer from damaged heart muscle which becomes scar tissue and fails to function properly. Now gene therapy research suggests that such scar tissue can be turned back into healthy muscle.

> Weill Cornell Medical College, Baylor College of Medicine and Stony Brook University Medical Center researchers have made a major advance in heart disease using gene therapy.The finding could mean a 'cure' for heart attack victims who suffer limitations.
>
> The scientists have found a cocktail of 3 genes that can turn scar tissue from heart attack back into a healthy functioning muscle. Adding one extra gene improved heart function in rats even more than anticipated.
>
> Findings published in the Journal of the American Heart Association, show adding a gene that stimulates the growth of new blood vessels enhances the effect of gene therapy for repairing damaged heart muscle.

And adapted genetic variants of viruses such as HIV are proving useful in unexpected ways. As The Los Angeles Times reported:

> Italian researchers have used a defanged version of HIV to replace faulty genes — and eliminate devastating symptoms — in children suffering two rare and fatal genetic diseases.
>
> Improved gene therapy techniques prevented the onset of metachromatic leukodystrophy in three young children and halted the progression of Wiskott-Aldrich syndrome in three others.
>
> The advance represents a major stride for a field that has struggled to translate experimental successes in lab animals into safe and effective treatments for people, experts said. Researchers may be able to use the team's method as a template, modifying it to treat a variety of diseases.

Despite being in its very earliest stages, the field of gene therapy is showing great promise.

"Designer Babies" Have Arrived

The tabloid press loves scary phrases such as "designer babies", "test tube conception" and "Frankenfoods". They're trying to scare their readers and, on the whole, their readers love to be scared.

It is now almost 40 years since the world's first" test-tube baby", Louise Brown, was born in the UK as a result of the now common procedure called in-vitro fertilisation.

Since that time a technology called "preimplantation genetic diagnosis", or PGD, has enabled In Vitro Fertilization (IVF) clinics to screen embryos for more than 100 potentially debilitating and often deadly diseases before the embryo is implanted into the mother. A medical revolution has thus unfolded, enabling literally tens of thousands of couples and their babies to sidestep some of the world's most terrifying diseases – nothing really scary about that![5]

But some people consider it unethical to use embryo screening (PGD) for other purposes – such as gender selection. In the UK and most other nations around the world it is illegal to screen embryos to select either a female or male embryo to implant in the mother's womb. But the process is wholly legal in the United States and it is becoming big business. As the website Singularity Hub pointed out:

> In many countries around the world PGD is heavily regulated and designer babies are strictly out of the question. Yet in a strange paradox, even as the United States is one of the world's most regulated nations in several areas of medical research and development, PGD is completely legal and unregulated in the United States. Hence, even as the United States is hindered by regulation in areas such as stem cell research, the country seems poised to be a world leader in the designer baby revolution.

> At the moment, The Fertility Institute carries the mantle as the company at the forefront of this revolution, and as such they are a lightning rod for the praise and adoration, but also the bitter and severe anger, of those on both sides of this great moral debate.
>
> Gender selection is a big business. Dr. Steinberg, Director at The Fertility Institutes, claims that they are performing on the order of 10 gender selection fertilizations every week, each for a fee of $18,400. Although In Vitro Fertilizations were originally designed to help parents that were unable to conceive children naturally, Steinberg says that a staggering 70% of their clients have absolutely no difficulty conceiving children, coming to the Institute purely for opportunity to choose the sex of their baby.
>
> The genie is officially out of the bottle, in fact it probably has been for a long time. There is no stopping the designer baby revolution. Even as some countries try to clamp down on it, others will allow it. Progress, if we call it that, will continue unabated. A similar phenomenon has unfolded with embryonic stem cell research in recent years. Even as the Bush administration almost completely strangled US investment and research in this promising field, other countries invested heavily and advances continued.
>
> A new generation of genetically enhanced designer babies is inevitable in the coming decades. Yet for those of us that are merely "normal", do not despair. Even as we are outmatched by the next generation genetically, a host of new technologies from chip implants to gene therapy may allow us to keep up, allowing us to enhance ourselves in equally transformative ways. The future will indeed be interesting.

If you decide to use the Fertilities Institute (or one of its competitors) to select the gender of your next baby, the cost for the service will be around $20,000. Like so much of future medicine, it will at first only be available to the rich.

The Future Of DNA-Based "Individualized Medicine"

Peering ahead to the year 2050 and beyond it is likely that most medical treatments will be based on our individual DNA profile. The long era of "one size fits all" medicine will be over, at least in the rich world. Drugs and

treatments will be tailored to us as individuals and will be many times more effective than they are today.

Most babies born in rich nations will arrive with their full genome decoded and I suspect that most adults will have their DNA profile stored in The Cloud (or whatever we are calling remote storage at that time), ready for access by physicians in case of need.

New DNA-based treatments (e.g. gene therapy) will be providing aids and cures to today's most vicious diseases and I suspect that even Alzheimer's Disease will have been brought under control.

As we understand more about DNA mutations I think it likely that cancer will have been relegated from a fatal disease to a manageable condition (this process has already started in developed countries) and typical longevity will have increased from today's 80 years to over 90 years . As I will discuss in later chapters.

Ends

[1] http://www.newscientist.com/article/mg21628952.200-fetal-healing-curing-congenital-diseases-in-the-womb.html?page=3
[2] http://www.independent.co.uk/news/uk/politics/100m-dna-mapping-project-for-cancer-patients-announced-8399066.html
[3] http://www.nytimes.com/2008/02/24/health/24dna.html?pagewanted=all&_r=2&
[4] http://www.conference.ie/Conferences/index.asp?Conference=161
[5] http://www.newscientist.com/article/mg21929252.800-designer-babies-are-on-the-horizon-but-arent-here-yet.html#.Ue1PO23-m1c