To What Extent Will the Incidence of Human Disease be Predictable from Genome Sequence Data and Genetic Screening? Will this Knowledge Generate an Uninsurable Underclass?

We look toward a future that promises the ability to predict our predisposition to a number of diseases from our genomes. With this knowledge, come social and ethical considerations, including the potential to discriminate against those with a 'bad' set of genes, such as through denying life insurance. The future potential to create an uninsurable underclass will depend greatly on the accuracy and extent of our predictive power – a matter of great speculation. However, cases of discrimination on the basis of genetic information have already been documented and government legislation is beginning to come into effect, restricting the use of genetic test information in insurance underwriting.

Introduction

Evidence from twin studies suggests that most human diseases have a significant genetic component – about 40-70% of our predisposition to disease is genetically determined[1]. Broadly speaking, genetic disorders can include[2]:

- Monogenic (single-gene or Mendelian) disorders, where the disease is caused by one or a pair of mutant alleles at a single gene locus. For the general population, the lifetime risk from these disorders is about 2%[3].
- Multifactorial (multi-gene) disorders, where variations in multiple genes (mutations or common alleles) lead to the disorder, often with a contributing effect from exposure to environmental factors, such as lifestyle, pollution and infections. These disorders are far more common than monogenic disorders, with an estimated 60% of the general population suffering from multifactorial conditions[3].
- Chromosome disorders, where there is an abnormal chromosomal constitution – rearrangement of chromosomal material or a gain/deletion of a whole chromosome or parts of a chromosome. These disorders arise during gamete production in meiosis rather than from heritable changes in DNA sequence and have not been included in the discussion of disease prediction.

The power of predictive genomics - the identification of the genetic predisposition of individuals to certain disease[4] - lies firstly in our ability to identify the genetic loci involved in producing the disease phenotype and secondly in our ability to accurately determine their relative effects in causing disease. The extent of our predictive power will then determine our potential to discriminate.

Genome Sequence Data and Defining Disease Genes

Human genome sequence data generated from the Human Genome Project (HGP) will be invaluable in the identification of disease genes. The past 20 years has seen an explosion in the identification of genes associated with Mendelian diseases, largely by positional cloning. Currently, around 1200 disease genes have been characterized[5],

including genes for cystic fibrosis[6] and breast cancer[7]. The value of human genome sequence data can already be seen in the positional cloning of hundreds of disease genes (Table 1). The cost of cloning individual genes has decreased roughly 100 fold using the methods and materials created by the HGP, seeing the transition from gene mapping methods based on the exchange of physical probes to a purely information-based technology, where physical maps consist of coordinates on the sequence itself.

Table 26 Disease genes positionally cloned using the draft genome sequence

Locus	Disorder	Reference(s)
BRCA2	Breast cancer susceptibility	55
AIRE	Autoimmune polyglandular syndrome type 1 (APS1 or APECED)	389
PEX1	Peroxisome biogenesis disorder	390, 391
PDS	Pendred syndrome	392
XLP	X-linked lymphoproliferative disease	393
DFNA5	Nonsyndromic deafness	394
ATP2A2	Darier's disease	395
SEDL	X-linked spondyloepiphyseal dysplasia tarda	396
WISP3	Progressive pseudorheumatoid dysplasia	397
CCM1	Cerebral cavernous malformations	398, 399
COL11A2/DFNA13	Nonsyndromic deafness	400
LGMD 2G	Limb-girdle muscular dystrophy	401
EVC	Ellis-Van Creveld syndrome, Weyer's acrodental dysostosis	402
ACTN4	Familial focal segmental glomerulosclerosis	403
SCN1A	Generalized epilepsy with febrile seizures plus type 2	404
AASS	Familial hyperlysinaemia	405
NDRG1	Hereditary motor and sensory neuropathy-Lom	406
CNGB3	Total colour-blindness	407, 408
MUL	Mulibrey nanism	409
USH1C	Usher type 1C	410, 411
MYH9	May-Hegglin anomaly	412, 413
PRKAR1A	Carney's complex	414
MYH9	Nonsyndromic hereditary deafness DFNA17	415
SCA10	Spinocerebellar ataxia type 10	416
OPA1	Optic atrophy	417
XLCSNB	X-linked congenital stationary night blindness	418
FGF23	Hypophosphataemic rickets	419
GAN	Giant axonal neuropathy	420
AAAS	Triple-A syndrome	421
HSPG2	Schwartz-Jampel syndrome	422

Figure 1 – Some disease genes positionally cloned using the draft human genome sequence

Figure taken from **International Human Genome Sequencing Consortium** Initial Sequencing and Analysis of the Human Genome 2001 *Nature* 409;860-921 (Page 912)

However, Mendelian inheritance is often not so simple, with clinical variability observed in many single-gene diseases. This is partly explained by mutational heterogeneity (different mutations within the same locus) but also by the effects of 'modifier' genes and environmental contributors[5]. Identifying such 'modifiers' is a large challenge and is closely allied with resolving the genetics of non-Mendelian disease, for which all contributing loci can be thought of as 'modifiers', as no single locus of large effect exists. Attention is now shifting to these more complex and more prevalent genetic disorders, such as cardiovascular disease, diabetes and schizophrenia[8]. It is clear that owing to weak linkage signals, positional cloning has limited use in their identification and attention has therefore turned to association or linkage disequilibrium studies. These large-scale genome wide studies[9] are only feasible in the wake of the completion of the HGP. Researchers have begun to establish a catalogue of all common variants in the human population, including

single-nucleotide polymorphisms (SNPs), small deletions and insertions, and other structural differences[10]. The HapMap Project[11] was formed in 2002, with a goal to characterize the patterns of linkage disequilibrium and haplotypes across the human genome and to identify the key SNPs that capture most of the information about these patterns. This information will enable large scale association studies that may identify the genes involved in multifactorial diseases.

The future should therefore see the identification of the majority of genetic loci implicated in disease. However, we may never be able to identify fully all of the genes involved in some multifactorial disorders, given the number of potential loci involved.

The genome provides the potential to develop certain diseases

The identification of all disease genes will not equip us *per se* with all the information required to accurately predict whether a person will develop a related disease. Our genes do not determine the diseases that we will develop; they merely predispose us to them. While there are a few genes for monogenic disorders that show almost complete penetrance (ability of a gene to express itself), such as cystic fibrosis, these are the exceptions[4]. Incomplete penetrance, as well as complicating factors, such as a variable age of onset (delayed onset may be caused by slow accumulation of a deleterious substance over time, such as cysts in adult polycystic kidney disease[2]) are often present with single gene traits[8]. The BRCA1 and BRCA2 genes (mutations affecting DNA repair implicated in breast and ovarian cancer) show both incomplete penetrance and late-onset[2,12] (Figure 1). These genes confer only a susceptibility; their effects are modified both by other genes and by lifestyle and environmental factors, giving rise to different quantitative levels of risk in different individuals.

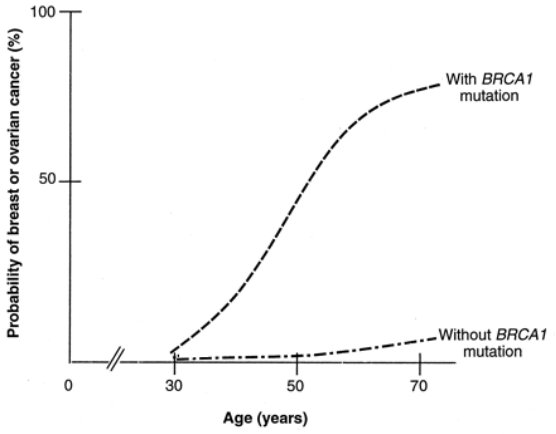


Figure 1 – Approximate chance of developing breast cancer by age with and without BRCA1 mutation. Even if it is known that a given gene variant is a predisposing mutation, accurate prediction of the individual's cancer destiny is not possible. Firstly, the risk has the dimension of time – even though the probability of cancer may be very high over a lifetime, it is still quite uncertain over the next 10 years. Secondly, the effects of predisposing genes are modified by other genes and by lifestyle and environmental factors, such as pregnancy or oral contraceptive use. The same mutation may, therefore, be associated with different quantitative levels of risk, and with predominant risks of different types of cancer, in different individuals even within the same family. Note also that the gene never reaches complete penetrance during an individual's lifetime.

Figure taken from: **Ponder, B.** Genetic testing for cancer risk 1997 *Science* 278;1050-1054 (Page 1052)

The more common multifactorial diseases involve the interaction of multiple genes and environmental factors[8]. The genome gives the potential to develop certain diseases and environmental and lifestyle choices act upon that potential. Coronary heart disease, which results from blockages in the arteries supplying blood to the heart, illustrates the interaction between multiple susceptibility genes and environmental factors[13] (Figure 2). A few types of coronary heart disease that are caused by single gene mutations have been identified, such as familial hypercholesterolaemia (FH) and hypertrophic cardiomyopathy (HCM) but most heart disease is caused by the inheritance of several different gene variants, each of which only has a small effect on heart function. Environmental factors contribute greatly to the disease and the combination of such variants and the 'wrong' environmental factors will increase the risk of heart attack

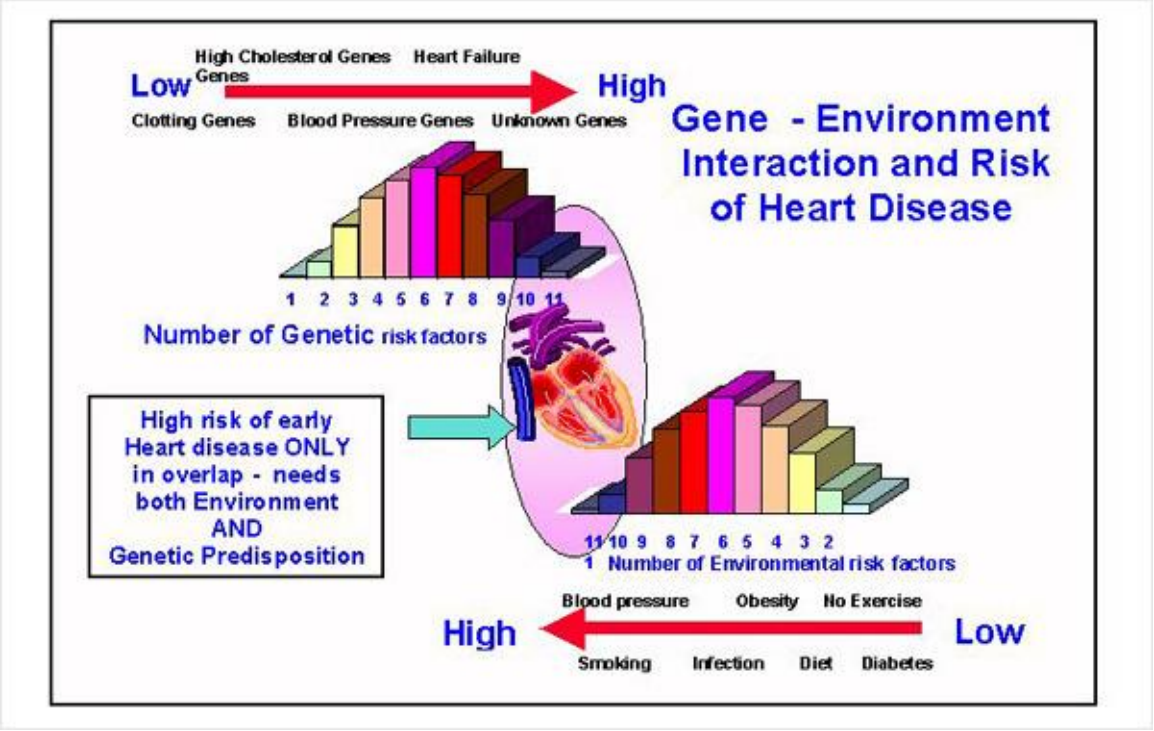


Figure 2 – Diagram illustrating the interaction between many genetic risk factors (susceptibility genes) and numerous environmental factors in the cause of coronary heart disease. Most heart disease is not due to a single mutation, as occurs in FH or HCM, but is caused by the inheritance of several gene variants, which might be involved in regulating cholesterol levels, blood clotting, blood pressure, etc., each of which only has a small effect on function. A combination of these variants plus the 'wrong' environmental factors will increase the risk of heart attack significantly. Examples of environmental risk factors are tobacco smoke, emotional stress (associated with a rise in blood pressure), lack of exercise, obesity, and poor diet.

Figure taken from *Window on My Life - The Sunday Times* 16/11/2003

As shown in Table 2, there is significant evidence for environmental contributions to complex diseases[14], with a specific requirement for environmental exposure for the development of several of the disorders, including AIDS, alcohol and nicotine dependence, and cervical cancer. For the case of nicotine dependence, although there is a genetic predisposition, the results of family and twin studies has

revealed that spouse correlations for nicotine dependence are equivalent to sibling correlations, indicating that the genetic dependence is a small factor when compared to environmental factors.

Table 1. Characteristics of Selected Complex Diseases

Disease	Phenotype measure	Genes		Specific environmental factors		Prevalence	Impact (DALY)	Ref.
		λ	Confirmed loci	Known?	Malleable			
Breast cancer	Biopsy	1.8	BRCA-1 BRCA-2	Parity, 1st child > age 30, physical inactivity	Possible	1.2%	0.4	(13, 18)
Alzheimer's disease	Clinical, neurocognitive testing, postmortem biopsy	2.8	PS1/PS2 APP APOE	Head injury, low educational level	Possible	5% (>age 65)	0.8	(14, 15, 41)
Type 1 diabetes	Immunologic markers, glucose metabolism	15.0	HLA INS	Nonspecific	No	0.4%	0.1	(17, 42, 43)
Multiple sclerosis	Clinical, neuroimaging	20.0	HLA	Nonspecific	No	0.2%	0.1	(6)
Autism	Clinical	60.0	None	No	No	.02%	No info	(44)
Schizophrenia	Clinical	9.0	None	No	No	0.8%	1.1	(45)
Cervical cancer	Biopsy	1.8	None	Human papilloma virus	Yes	0.16%	0.3	(18)
Type 2 diabetes	Glucose metabolism	4.3	PPARγ	Obesity, physical inactivity	Yes	6.1% (>age 20) 15.0% (>age 60)	1.1	(19, 46)
AIDS	Clinical, antibody, $CD4^+$ count	NA	CCR5 HLA	HIV	Yes	0.12%	6.0	(47, 48)
Nicotine dependence	Interview	1.4	None	Nicotine	Yes	24.0%	–	(9, 49)
Alcohol dependence	Interview	7.0	ADH2 ALDH2 (protective)	Alcohol	Yes	4.0%	4.2	(50, 51)

Table 2 – Some complex diseases with specific environmental factors

Table taken from: **Merikangas, K. R. & Risch, N.** Genomic priorities and public health. 2003 *Science* 302;599-601 (Page 600)

Therefore, it may not be easy to predict the incidence of disease (with an identified genetic component) from genetic screening and the identification of particular disease gene variants. The extent to which disease will be predictable questions the power of predictive genomics and its consequences for humanity.

Large population-based studies have been proposed to try to increase our predictive capacity, such as the UK Biobank Project[15] due to start early in 2004. The collection of extensive clinical information and ongoing follow-up could be used to obtain unbiased assessments of the relative disease risk that particular gene variants contribute[10].

Predictive genetic testing in the present day

Predictive genetic tests are available for assessing susceptibility to a variety of diseases, including haemachromatosis, breast and colon cancer, and Alzheimer's and Huntington's disease[16]. These test for the presence of the common variants of normal genes known to be associated with a disease state. Predictive genetic tests assess asymptomatic persons for future health problems. This is a process that is distinct from genetic tests such as those used for heterozygote carrier testing, for example in carriers of sickle cell trait[17], or to confirm a suspected diagnosis, such as the fragile X syndrome in a developmentally delayed child[18].

Genomic sequence data and an increase in our understanding of multifactorial disease (e.g. from association studies) is opening the door for the development of new commercial predictive genetic testing methods. Now, physicians and consumers can order personalised genomic profiles as a means to identify individual risk, for the purpose of tailoring specific risk-reducing actions, such as dietary modifications, that

are expected to prevent disease[19]. Genomic profiling consists of the concurrent detection of multiple gene variants that have been associated with a greater risk or predisposition to a particular disease. These profiles test for the presence of a number of SNPs, which are the most common polymorphism present in the genome and are believed to be associated with almost all diseases[20]. Great Smokies Diagnostic laboratory[21] offers four predictive genomic panels (each contains a dozen or so of the more common SNPs): a cardiac risk panel, an osteoporosis risk panel, an immune function panel and a detoxification panel. For instance, the cardiovascular risk panel identifies SNPs associated with increased risk of developing coronary artery disease, hypertension and other vascular diseases, measuring markers for risk factors including inflammation, folic acid defects and iron storage problems.

However, Burke et al. have recently commented, "Although genomic profiling may *ultimately* provide a sound basis for personalised lifestyle modification…the science is still in the early stages of deciphering gene-gene and gene environment interactions and their health implications. At present, the evidence to support genomic profiling is weak."[19]

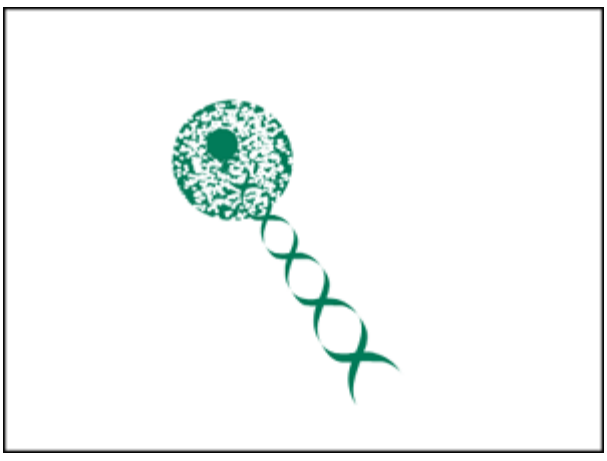
Toward a future of predictive genomics

The next step forward in predictive genomics will be the ability to sequence the genomes of particular individuals quickly and cheaply. In a speech to the Royal Society's People's Science Summit, Sir Paul Nurse of Cancer Research UK said he could foresee a time in the future – perhaps within 20 years – when the entire genetic code of every newborn baby would be recorded[22]. In fact, Craig Ventor is already offering people the opportunity to have their genomes sequenced in a week for £450,000[22] and a British company, Solexa, have developed a method, which they call Single Molecule Array Technology[23] (Figure 3), with the ultimate goal that they will be able to sequence an individual's genome in 24 hours for $1000 (~£550)!

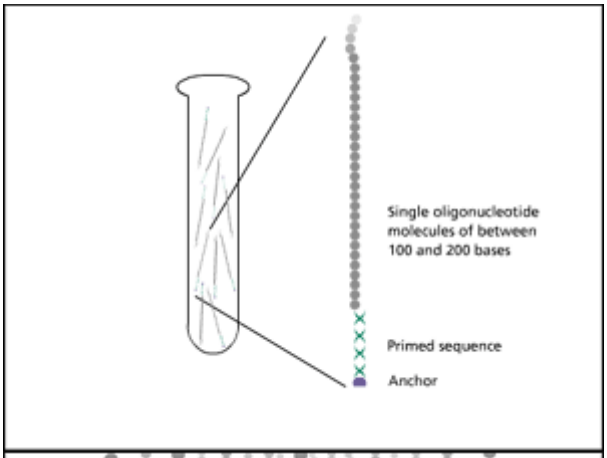
This information would be the ultimate luxury for the predictive clinician, allowing the measurement of virtually all differences/polymorphisms (e.g. SNPs) between an individual subject sequence and a reference sequence, with no *a priori* choices required about where relevant variations are assayed.

Figure 3 – Solexa's Single Molecule Array technology for genotyping of an individual

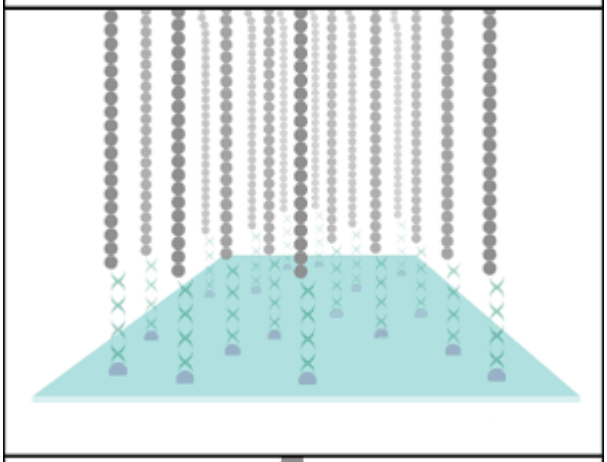
Taken from Solexa website http://www.solexa.co.uk/technology/how.htm



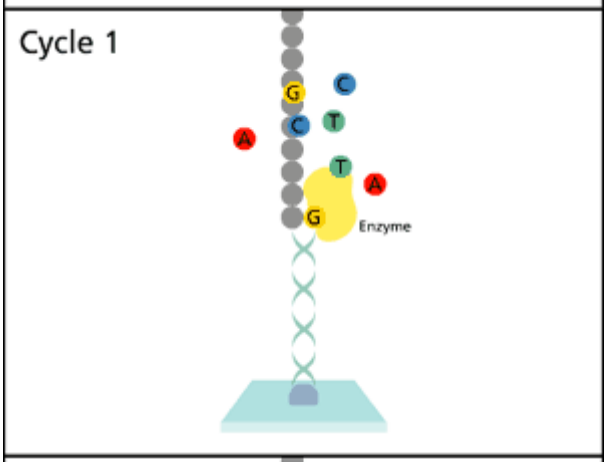
Genomic DNA is extracted from sample cells taken from an individual.



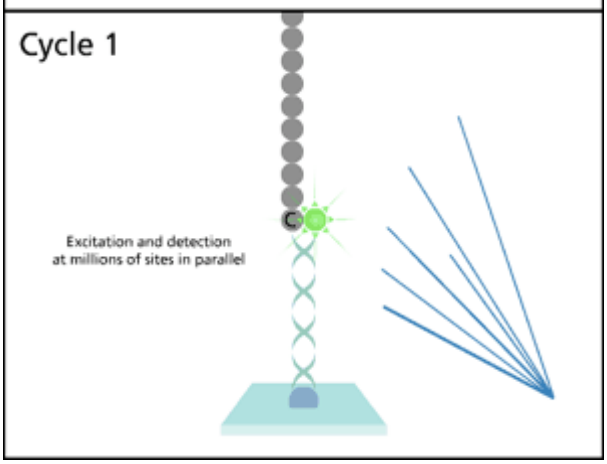
In a single tube reaction, genomic DNA is processed into single-stranded oligonucleotide fragments. These are prepared for attachment to Solexa's Single Molecule Arrays using proprietary primer and anchor molecules.



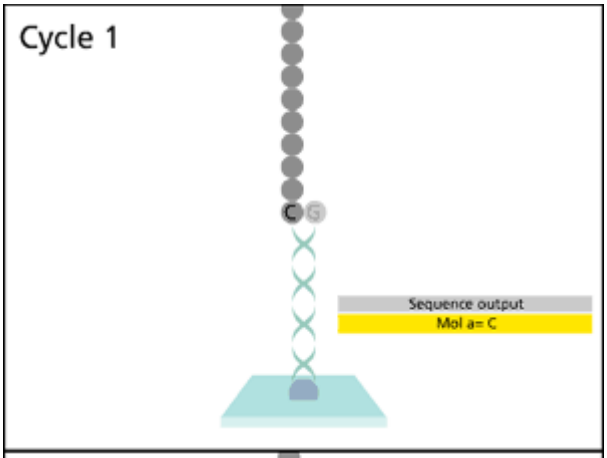
Hundreds of millions of molecules, representing the entire genome of the individual, are deposited and attached at discrete sites on a Single Molecule Array.



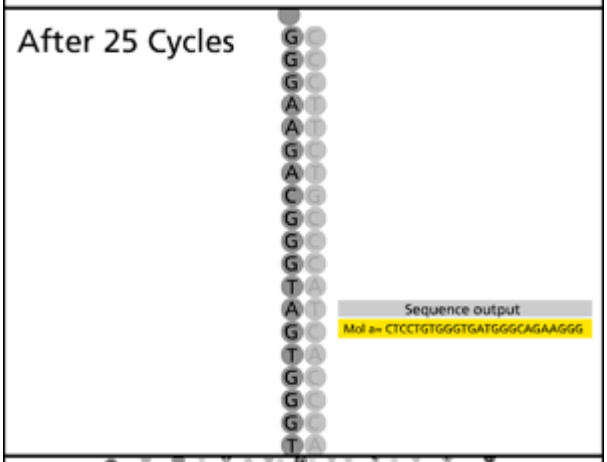
Fluorescently labelled nucleotides and a polymerase enzyme are added to the Single Molecule Array. Complementary nucleotides base-pair to the first base of each oligonucleotide fragment and are added to the primer by the enzyme. Remaining free nucleotides are removed.



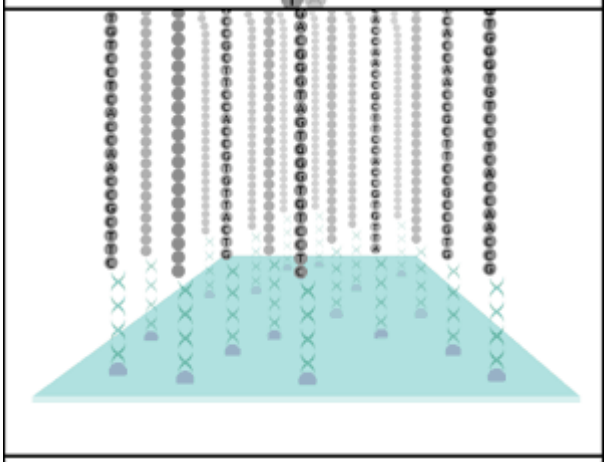
Laser light of a specific wavelength for each base excites the label on the incorporated nucleotides, which fluoresce. This fluorescence is detected by a CCD camera that rapidly scans the entire array to identify the incorporated nucleotides on each fragment. Fluorescence is then removed.



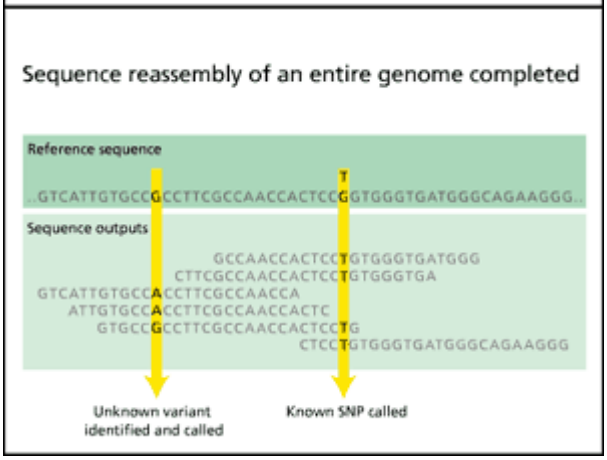
The identity of the incorporated nucleotide reveals the identity of the base in the sample sequence to which it is paired. In this example, the first base is C (cytosine).



This cycle of incorporation, detection and identification is repeated approximately 25 times to determine the first 25 bases in each oligonucleotide fragment.



By simultaneously sequencing all molecules on the array the first 25 bases for the hundreds of millions of oligonucleotide fragments are determined.



These hundreds of millions of sequences are aligned and compared to the reference sequence using Solexa's proprietary bioinformatics system. Known and unknown single nucleotide polymorphisms (SNP's) together with other genetic variations can then be readily determined.

Genetic Testing and Insurance

Predictive genetic testing may have serious implications for insurance, particularly life insurance and health insurance (not significant in Britain due to the National Health Service). Furthermore, there may be implications for other forms of insurance, such as car insurance, where an asymptomatic person with a predisposition to a heart condition might be denied insurance or have to pay a higher premium, as this might pose a danger when driving. There may also be other consequences of open genetic information. For example, employers might discriminate against people with a predilection to alcoholism, and finance companies might deny mortgages or loans based on a predictive disease state or life expectancy.

The insurance industry is based on the principle of equity[2], where people with equal health/life expectancies pay equal premiums, while those having worse health or lower life expectancies pay higher premiums for life or health insurance. It works on the basis of a mutual risk pool in which members contribute according to the risk they bring to the pool. The insurer underwrites to classify each applicant into different risk groups.

Currently, medical information (e.g. HIV status, serum cholesterol levels and blood pressure) and family history (e.g. inherited diseases such as breast cancer) are used in the underwriting process[16]. Similarly, an insurance company might also like to consider a genetic test for underwriting. If, however, consumers withheld genetic information from insurers, this would result in antiselection, destabilising the equity principle[2]. Mary Francis, Director General of the Association of British Insurers, on the subject of genetic testing, commented to the BBC that, "If there is evidence that someone might develop a disease, we have to take that into account."[25]

Laws governing genetic testing

Insurance, through the risk classification process, *is* discriminatory and there have been numerous debates over whether insurance companies should be allowed access to genetic information for underwriting. In the UK, there is currently a moratorium on the use of genetic test results that will last until 2006[26]. The moratorium applies to life insurance policies up to £500,000 and other insurance policies, e.g. income protection policies, of up to £300,000. For policies above these limits, insurers may only use results of tests approved by the Genetics and Insurance Committee (GAIC). Currently, the only authorised test is for Huntington's disease, although there have been other genetic tests recommended by the ABI as relevant for insurance purposes[27]. Furthermore, under the ABI Code of Practice on Genetic Testing (1997), insurers cannot require applicants to undergo a genetic test to obtain insurance[28].

In other countries, such as Austria and Belgium, the use of genetic information for any business purpose is not allowed[2]. In the US, the Senate has recently passed the Genetic Information Nondiscrimination Act of 2003[29], which prevents health insurers and employers from using genetic information to determine eligibility, set premiums, or hire and fire people.

Will our predictive power generate an uninsurable underclass?

There is already a history of cases where genetic information has been used to discriminate against people in insurance cases, such as in the early 1970s where some insurance companies in the US denied coverage and charged higher rates to carriers of the gene for sickle cell disease, even though they were healthy[30.] Cases have also been documented in the US where healthy people were denied health insurance from predictive genetic test results, despite taking preventative health measures based on their test results[31]. In the UK, insurance companies have used genetic test results for Huntington's disease to calculate or refuse premiums[32].

Whether the ability to predict disease will create an uninsurable underclass may firstly depend on laws governing the availability of the genetic test information. If the idea of 'Genetic Exceptionalism'[16] is accepted, where genetic tests for disease prediction are considered unique from non-genetic predictive tests, such as serum cholesterol level, then we do not have to worry about discrimination as test results will be kept private and used only for treating the patient.

While legislative restrictions may suppress the formation of a genetic underclass, there have been numerous reports which suggest that fears of a genetic underclass are unfounded. Dr. Angus McDonald has conducted mathematical research on the additional expense on the carriers of the ApoE ε4 gene, which gives an increased risk of developing Alzheimer's disease late in life[33]. His modelling shows that for the 2% of the population which carries this gene, the result will be an increase in their healthcare costs of between 10 and 30%, which only puts them on the borderline of having to pay increased premiums. Also, if genetic tests meant that medical care could improve the health of the patient, their long-term health care costs could be reduced. Dr. MacDonald also claims that the extra health care costs of many disease genes are less than other risks that insurance companies ignore, such as playing sport.

In the future we may all have our genomes sequenced. If this sequence data is freely available and open for use in insurance underwriting, the extent to which a genetic underclass might be generated will ultimately depend on our ability to be able to accurately predict the incidence of disease from this information or any other genetic screening procedure. However, even the prediction of single-gene diseases is prone to complications and there are relatively few genes with 100% penetrance that could be used to heavily discriminate against individuals. Many people with these highly penetrant genes are already discriminated against through their family history and the advent of genetic testing will probably not create new groups of discriminated people. Also, in the meantime, before full-scale genomic sequencing of the whole population is introduced, these are the most likely people to undergo testing. Here, a negative test result would make them far more insurable, rather than creating a new underclass.

The prediction of the far more common diseases, such as coronary heart disease, that affect a greater amount of the population, poses an even greater problem. If insurance underwriters wanted to use predictive genetic testing then the predictions would have to be accurate, so that they could be classed as 'fair' discrimination and suitable for use in underwriting. This would probably also rule out being able to discriminate against people that have predilections to diseases that require a significant environmental input or lifestyle choice, such as alcoholism or nicotine addiction.

I believe that disease prediction will probably turn out to be too complicated for us to *accurately* predict the incidence of most diseases with a genetic component, including both multifactorial diseases as well as a number of monogenic disorders, and as such I would suggest that there would be little potential to create an uninsurable underclass. However, it could be argued that the potential for an uninsurable underclass might actually be greater if only a few instances of disease were predictable, allowing heavier levels of discrimination to be levelled upon the few individuals with these rare genes.

Even if in the future the ability to predict the more common, multifactorial diseases does become a reality, we all posses dozens of glitches in our genomes that probably predispose us to a great number of diseases and it will again be difficult to discriminate between different people. Furthermore, if we do reach a stage where common diseases are easily predictable, surely the level of understanding that we would then hold would lead to the development of effective treatments, such as gene therapy, and the abolition of any genetic underclass.

Word Count: 2993

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