

Personalised Medicine in New Zealand – Think Piece

September 2012

Background

Personalised/Precision/Genomic medicine (for simplicity, PM) may be thought of as the delivery of the right drug (or intervention) in the right dose to the right person at the right time, based on each individual's personal genetic and disease characteristics.

The Genomics and Medicine Act of 2007¹ enacted by the Senate of the USA aimed “to secure the promise of personalized medicine for all Americans by expanding and accelerating genomics research, to improve the accuracy of disease diagnosis, increase the safety of drugs, and identify novel treatments.” It went on to define personalised medicine as “the application of genomic and molecular data to better target the delivery of health care, facilitate the discovery and clinical testing of new products, and help determine a person's predisposition to a particular disease or condition.”

PM seeks to deliver on the promises of the last 15 years of medical progress. The completion of the Human Genome Project (2001) promised a new understanding of the fundamental basis of disease.^{2,3} It was predicted that by understanding the ways in which DNA is altered the causes of disease could be elucidated, and future treatments would be revolutionised.⁴ This new paradigm of health care would mean an active treatment could be prescribed for each patient on the basis the specific genetic characteristics of his or her disease.⁵

Targeting treatment at specific drivers of disease was not a new idea. As early as the turn of the 20th century it was known that removing women's ovaries (and thereby reducing the female hormones) could induce a temporary reduction in the burden of breast cancer, but it was not until the mid-1990s that the first antibody specifically aimed at a molecular target (trastuzumab or Herceptin®) entered clinical practice.⁶⁻⁸

Crash Course in Genomics

(Genetics terminology in italics)

Genomics is the study and exploration of genes, and how they interact with each other and the environment across all a species' genes (the *genome*). This section will provide an overview of our understanding of genomics as it exists today.

Genes are coded by series of DNA molecules that link to form the famous double-stranded helix of Watson and Crick. This DNA is stored in the nucleus of each of our cells in the form of 23 pairs of chromosomes (i.e. 46 chromosomes in total). We receive one copy of each chromosome (containing different forms of the same genes, termed *alleles*) from each parent, and although initially not thought important some genes are expressed only from maternal or paternal genes (termed *imprinting*).

DNA consists of connected sequences of four particular molecules, called *bases* or *nucleotides* (adenine – A, tyrosine – T, cytosine – C, guanine – G). A binds exclusively to T (A-T) and C to G (C-G) to form “*base-pairs*” (bp). The DNA in genes was for many years thought to code only for protein synthesis, although we now know this to be incorrect.

However, protein synthesis is still a crucial component of DNA function. The DNA is copied into RNA (*transcribed*) and then transported from the nucleus into the cell where part of the gene's RNA is removed from the sequence (*splicing*) to leave only the part required for the protein encoded – this part of the gene

is termed the exon (i.e. the part that is directly turned into protein). All the exons across the entire genome are called the *exome*. The vast ranges of proteins they encode in our bodies are called the *proteasome*.

The DNA exons, read to produce proteins (*translation*), are coded in 3 bases sequences, called *codons*, which represent each of the 20 amino acids. The order of these codons determines the structure of these complex proteins. There is redundancy in the number of potential 3-letter sequences (i.e. ATT, ATA & ATC all code for isoleucine). This means some *point mutations* (individual base alterations, e.g. an A-T base-pair is mutated to a T-A) are *silent*, whereas as others significantly alter the genetic coding, subsequent protein. For example, a *deletion* mutation may cause a “*frame-shift*”, where a base-pair is completely removed from an exon causing the subsequent codons to code for incorrect amino acids, or the formation early abnormal early stop signal (e.g. TAA, TGA, TGA tell the enzymes to stop transcribing DNA). These mutations completely change the structure of the relevant protein. A clinical example of this is the abnormal dystrophin protein seen in Duchenne’s or Becker’s muscular dystrophy.

The parts of DNA between exons are called *introns*. These were previously thought to be “junk” DNA, present to make the DNA more able to withstand mutation or perhaps redundant genes that through evolution were retained but which were no longer useful. In fact, perhaps unsurprisingly, they are crucial to DNA function. These are now known to be important in controlling how much and which parts of genes are transcribed, and in fact may be transcribed into RNA and may act directly on cell and DNA function, without needed to be translated into proteins.⁹ To add to the complexity methylation and acetylation of structurally normal genes affect the expression of them.⁹ Therefore, the range of mechanisms of disease at a genetic level is complex and our understanding continually evolving.

Mutations are vitally important, and until we understand the role of RNA and other forms of gene regulatory abnormalities more fully, they remain the key to our understanding of disease. Mutations are changes to the “normal” sequence of DNA. This in itself is a difficult definition because there are many differences in each of our genetic sequences that just represent normal variation. We all have many individual base-pair differences (called single nucleotide polymorphisms or variations, SNP/SNVs).¹⁰ Some of these are important and lead directly to disease, but most do not. These SNPs may lie close to other important mutations, however, and many experiments have sought to *associate* SNPs with disease to allow us to test for them (i.e. if patient X has symptoms consistent with disease Y we can test for a SNP known to be associated with that disease to confirm the diagnosis). When these SNPs are looked at across our entire genetic material this is termed *genome-wide association studies* (GWAS).

It becomes clear that there are many different mutations that may lead to the same disease. This idea becomes more complex when we consider cellular communication pathways. Imagine you are in traffic jam on a road with a number of traffic lights – it does not matter which of those traffic lights is faulty, the result is the same, your 15 minute commute now takes 3 hours. Similarly in cells, mutations in genes coding for any of the proteins in pathway of communication can result in a similar disease (e.g. an EGFR mutation might cause the same cancer as a mutation in the other signalling proteins in the pathway e.g. RAS, RAF or MEK).

Mutations can either be passed on at birth (*germline mutations*) or occur through life in our interaction with the environment (*somatic mutations*). Cancer provides numerous examples, BRCA abnormalities are germline and predispose for a risk of multiple cancers, whereas as carcinogens in cigarettes causes somatic mutations in otherwise normal cells. Some diseases are simple where a single mutation causes the disease (e.g. cystic fibrosis caused by a deletion mutation in the sodium-chloride ion channel), whereas otherwise are more complex (e.g. cancer development requires a number of mutations in perhaps 10-20 genes to overcome a cell’s protective mechanisms). Also, it is not only an abnormal sequence that causes disease but the number of copies of a gene can also be important (HER-2 overexpression in breast cancer). This complexity is perhaps the greatest challenge to our understanding and application of genomic information to the treatment of disease.

Genomic Testing

The cornerstone of this new paradigm is the ability to rapidly sequence the entire human genome, an increasing understanding of it and how mutations within its individual genes drive disease. This allows targeting of these abnormalities with specific treatments (at least theoretically).

The well-publicised Human Genome Project first published a draft sequence of the human genome in 2001,^{11,12} and successfully completed it in 2003,¹³ at a cost of US\$75 million. In doing this, they were able to map each of the components of DNA that constituted all a person's genes (i.e. approximately 3.1 billion base pairs). With this came the hope that our understanding of disease, its causes and treatment would be fundamentally altered.^{4,14}

The National Health Committee's experience with the EGFR project has given the Committee an insight into many of the issues of testing in this new era. EGFR can be tested for in many different ways and the range of tests is vast and applies to all other genetic diseases. Below is a summary of common types:

- **Immunohistochemistry (IHC):** an antibody is directed against a known target in or on cells. The antibody has an enzyme attached which then allows a stain or fluorescent signal to be produced highlighting areas and density of attachment. This can be seen with a microscope.
- **Fluorescent in situ hybridisation (FISH):** DNA *probes* with attached fluorescence are directed at known sequences of DNA. This often involves two probes directed at different areas of DNA to identify abnormal fusion mutations (where two genes that are usually separate have become joined causing disease) – thereby a red probe and a green probe are seen together as a yellow signal identifying the abnormal fusion.
- **Enzyme-linked immunosorbent assay/Enzyme immunoassay (ELISA/EIA):** uses antibodies to identify chemicals or proteins in blood or tissue (e.g. can identify hepatitis C antibodies by using antibodies directed at them), and using attached enzymes to produce a detectable signal.
- **Polymerase chain reaction (PCR):** single strands of DNA are copied by adding the DNA polymerase enzyme and the strand of DNA in question to a solution of free nucleotides (A,T,C,G) which then form a mirror of the DNA and are able to be read.
- **Microarray:** small DNA probes are arranged in wells and the sample DNA is added. Binding of DNA from the sample causes fluorescence in each well, with the intensity of signal indicating the amount of DNA bound. This allows for multiple different probes to interrogate the sample DNA at one time – it allows for analysis of gene expression (i.e. which genes are being used and which aren't, especially useful in cancer).

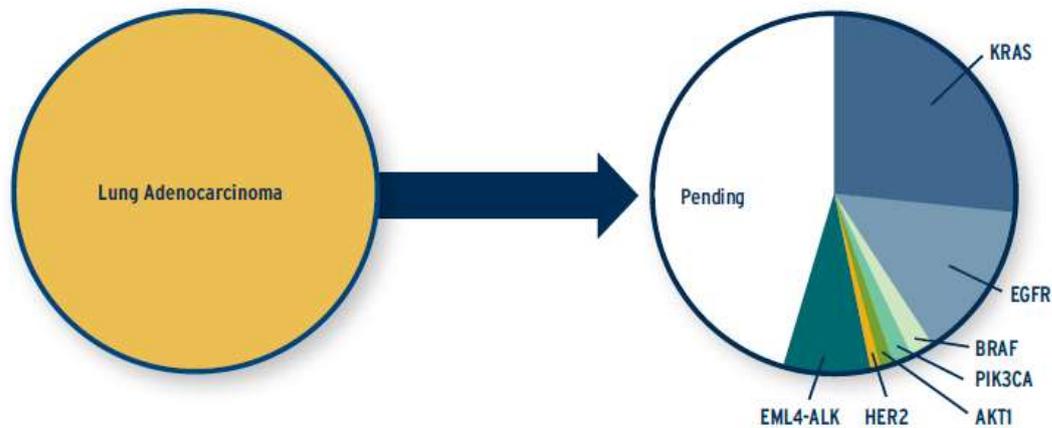
PCR and microarray most accurately analyse DNA but are costly. The other methods are less costly but rely on knowing the target protein or DNA sequence.

Again lung cancer is informative in this area. When testing for EGFR there are the options of more targeted tests to look at specific exons for known mutations, or a comprehensive (and more costly) PCR of the whole gene. As the National Health Committee has learned with EGFR accuracy, i.e. sensitivity and specificity, as well as the frequency of the abnormalities affect the performance of each test. We also know that there are an increasing number of mutations which drive lung cancer, let alone every other disease (see figure below). These genetic mutations which drive disease and can be treated require *companion diagnostic tests*, because without the test there is no treatment. The drug and test are inextricably linked.

Cancer in the Molecular Era: Identifying the Drivers of Lung Cancer

BEFORE: One Disease

TODAY: Many different forms of lung cancer driven by different molecular defects – with more yet to be identified



ASCO's Blueprint for Transforming Clinical and Translational Research

9 15

Currently, tests aimed at identifying one genetic abnormality are in use but these may not serve us in the future, for two main reasons: cost and flexibility. The issue of cost is best illustrated by an example; ROS1 is a recently discovered driver mutation in lung cancer that affects 1% of all lung cancer patients. A test to diagnose this mutation may cost \$1,000 (hypothetical cost), but in order to diagnose one patient one must conduct the test on 100 patients i.e. the cost to diagnose one patient with a ROS1 mutation is \$100,000 not \$1,000.

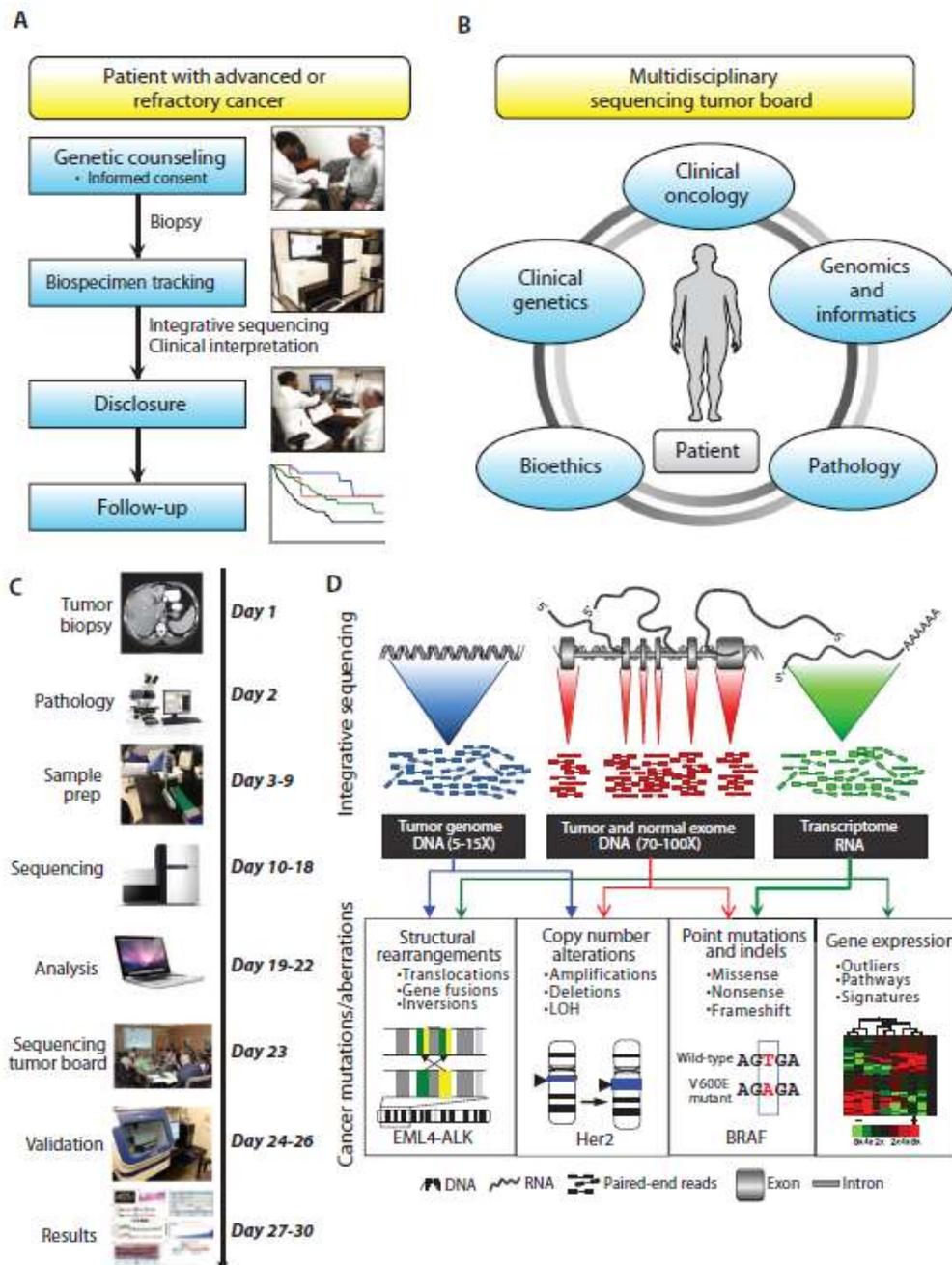
Then consider that each person's tumour may need to be tested for 20 or more mutations to find the best combination of medications for his/her tumour. Tests aimed at individual mutations will not identify novel mutations, mutations in other proteins or other contributing mutations which drive a patient's disease (i.e. a patient may have more than one driver mutation). Tests aimed at specific mutations, even a wide array of mutations, will miss important information. Not to mention, as we learned earlier, gene copy number, RNA and protein expression, all of which are critical to understanding and diagnosing disease.

The first human genome cost US\$75 million to sequence and as little as 4 years ago it cost US\$200,000 to sequence a genome.¹⁶ It now costs approximately US\$5,000-10,000, and the price has been falling exponentially in recent years. This next-generation ("next-gen") sequencing allows for quicker and more accurate analysis of the entire genome. Predictions are that whole-genome sequencing will cost under US\$1,000.

To illustrate simplistically how this might be used in practice in the future note the diagram from a pilot study from Roychowdhury et al.¹⁷ A patient with cancer might present. A swab of their inner cheek allows sequencing of their "normal" genome, which is then compared to their "tumour" genome to analyse the acquired genetic changes. A further analysis of their exome is completed to look for copy number abnormalities and mutations. Finally, RNA expression is analysed to check which genes are actually activated and to what degree. In doing this one understands the cancer in the context of the patient's genetic background, the possible activating mutations and which genes are actually important in disease promulgation. In theory this allows the doctor to then choose the most appropriate treatment regimen for the individual patient. As with EGFR the quality assurance of testing is vital and validation of laboratories equally important.

What is also well illustrated in this diagram is that the PM is not just about a test and a drug, but requires a whole model of care. It involves planning who takes the biopsy and how much tissue is needed (surgeon, radiologist, pathologist or diagnostic-physician), how is that tissue processed and stored (pathologist and laboratory technicians), where the enormous quantities of information is stored (organisational/regional/national databases), how that data is communicated and interpreted (physician, surgeon, multidisciplinary meeting, GP) and communicated to the patient and family (doctor, genetic counsellor).

The question also arises of which parts of the genetic information received can and should be communicated to each patient. There will be innumerable abnormalities that will not be able to be interpreted or will be of uncertain significance. There may be known mutations that may affect a patient's or patient's family's future risk of disease. These new bits of genetic information may not be welcomed.



Tissue Handling and Storage

Tissue handling and storage becomes fundamental to the practice of PM, because within each tumour/cell resides the crucial information required to understand the disease.

Currently, only a small piece of each cancer removed is analysed and stored for future reference. These samples are usually fixed in paraffin and can be potentially stored “forever” in off-site storage facilities to allow for re-interrogation of the sample. However, the rest of the tissue is either destroyed or returned to the patient (particularly important to Maori). The potential value of this tissue is significant.

In some international research institutes the lack of high-quality tissue matched with clinical information available for research, means the institute may be willing to pay up to US\$1,000 for a piece of tumour tissue, and US\$10,000 for a piece of tissue and matched clinical information. A cancer cliché heard at conferences around the world is: “tissue is the issue”.

Data

With this increasingly powerful testing the resulting volume of information requires improved data storage and handling. Privacy and access become crucial aspects to this aspect of PM.

Bioinformatics is the application of statistics and computer science to the field of molecular biology. With the vast amounts of data generated by these new techniques, bioinformatics’ role will expand. It allows interpretation and analysis of the data collected and has been developing as the science of genomics has evolved. This is currently being done in research labs in New Zealand and other labs around the world. It serves to illustrate that integration of multiple disciplines will be brought to bear on future medicine.

One important aspect of PM is how to communicate, display and interpret the overwhelming quantity of information. There are approximately 3-5 million SNPs in the human genome,¹⁰ only some of which are important in disease states. Other mutations, copy number and expression profiling need to be interpreted in concert. A platform that allows communication of what is and isn’t important or interpretable (i.e. we don’t know what all mutations mean, if anything) is needed to be able to provide patients with relevant information.

Interpretation and communication of relevant abnormalities in a way that can be understood and used in a practical way is another barrier that will have to overcome to allow this to be used at the coalface.

Clinical Trial Design and Flexibility

PM is fundamentally altering clinical and research trials. Rather than comparing a treatment across groups defined by the presence of a broad disease state, increasingly the understanding that many genomic abnormalities can result in similar disease states means treatments will be targeted at genomic states rather diseases (i.e. EGFR-mutated cancer of lung, colon and breast, rather than just breast cancer of any sort).

The American Society for Clinical Oncology (ASCO) published its “Blueprint for Transforming Clinical and Translational Cancer Research” in 2011,¹⁵ which sought to establish the future direction of cancer trial design and conduct. It stresses the importance of biomarkers (i.e. substances or biological features that can be easily identified and used to diagnose and/or monitor disease, e.g. cholesterol for heart disease or EGFR mutation in lung cancer). This should allow improved diagnosis, monitoring and more targeted treatment of cancers.

ASCO also predicts that in the next 10 years, new trials of medication will be directed at smaller parts of a disease population. Trial populations will be selected on molecular characteristics; only treatments with a high chance of success will be trialled, enabling smaller and faster trials. Adaptive trial design will allow for trials to be modified as new information becomes available, so large expensive trials are not having to be constantly repeated with minor variations. Co-operative groups and international collaboration will be required to allow recruitment of sufficient patients with rare abnormalities. Clinical trial documentation (potentially through clinicaltrials.gov) will be fuller to prevent wastage of resources through duplicate trials across groups.

Increasingly, participation in clinical trials will become the standard of care, as treatment evolves rapidly and individually. Here again the collection of real-world, real-time data will be invaluable.

Consent, Disclosure and Ethics

Genome based testing requires a new approach to consent, disclosure and ethics. The dilemma is rooted in the ability of genomic testing to reveal genetic alterations that predispose but do not guarantee disease; complex interactions between genetic predispositions that are difficult to interpret; unexpected mutations that may impact on other areas of health; mutations that may not impact on the patient but on their children instead; and, the use of genetic information to discriminate, either explicitly or implicitly.^{18,19}

These ethical dilemmas can be divided into three areas: physician-patient relationship; privacy and prevention of discrimination; and public health.

The physician-patient relationship is altered in many ways. Genetic counselling becomes crucial. There is a chance of uncovering a high-risk for a serious disease, which may be untreatable – this is especially difficult if the disease is not fully penetrant (i.e. for example only 50% of people with the gene go on to develop the disease). Some genetic abnormalities may have reproductive implications, and others have implications for offspring rather than those tested (e.g. BRCA mutations in a male). Genome sequencing may uncover a whole raft of data that is difficult to interpret and even more difficult to communicate. Physicians will have to be able to interpret and explain these ever more complex results. This makes direct-to-consumer genetic testing an uncomfortable rabbit that has already been pulled from its hat.

The use of genomic testing requires an adapted understanding of our rights to privacy, autonomy and full disclosure. In thinking about privacy a number of crucial questions arise. Who should have rights to this information and in what form? Should our genetic material be stored or returned to us (particularly important for Maori)? Should physicians be compelled to inform family members of genetic risk (even if incomplete)? Discrimination based on genetic information is an enormous concern to patients. We have to consider, albeit to a lesser degree than countries that rely much more heavily on health insurance, the impact on the health insurance industry in NZ.

Public health is also an area of consideration and the relationship of the government to its citizens. If a state-run health system mandates genomic testing in some circumstances it then bears the responsibility for acting appropriately on the results. It requires a responsible, transparent and defensible approach, especially if testing is not voluntary. Prevention is another issue, as genomic testing may allow us to better understand our predispositions to disease, but to what degree should public health initiatives have access to our individual data. The line between public health prevention and personal intervention will become more blurred.

International

Norway announced earlier this year that it was set to become the first country to incorporate genome sequencing into its national health service.²⁰ The Norwegian Cancer Genomics Consortium has begun a 3-year pilot phase. Norway has a population of 4.8 million.

It plans initially to use “next-gen” sequencing to test the tumour genomes of 1,000 patients, and 3,000 previously obtained biopsies in the initial phase. The second phase aims to build clinical, laboratory and computing capability to bring the technology to the approximate 25,000 Norwegians diagnosed every year. The predicted cost of the project is US\$6.3 million.²⁰

In a similar pilot in the UK, the Stratified Medicine Programme, Cancer Research UK is working with AstraZeneca, Pfizer and other UK government agencies to test 9,000 patients’ tumour samples at centralised laboratories during the pilot phase (July 2011 – July 2013). Collection and storage of information will be done by their Cancer registries.^{21,22}

New Zealand Perspective

This type of approach is only being undertaken in research settings in New Zealand, although in the near future there may be a move by academic physicians keen to bring cutting edge research to New Zealanders to push this agenda in to the clinic environment.

It is inevitable that medicine will move down this path, and not only in cancer, although it will be one of the disciplines leading the way. There are many examples of PM in other disease states, for example Vertex pharmaceuticals have just produced a molecularly targeted drug (ivacaftor) in cystic fibrosis at US\$294,000 per year.

We have an opportunity in New Zealand to harness this new paradigm. Our size and nationalised health service may benefit us in this endeavour. NHI numbers allow unique and consistent identification of each patient, and information gathering and integration of data collection from the private sector could aid this further. By pooling resources across the country and developing a national, concerted approach to tissue storage and maintenance, data collection, and incorporation of clinical information we can create a powerful tool. If done correctly, this would make NZ an attractive collaborator for overseas groups and institutions, and an even more attractive setting for future clinical trials. The knock-on effect will be a strengthening of our academic institutions, encouragement for some of our brightest and best scientists to return here, and potentially commercial opportunities as yet unforeseen.

Glossary of Genetic Terms

Allele: An alternative form of a gene.

Alternative splicing: A regulatory mechanism by which variations in the incorporation of a gene's exons, or coding regions, into messenger RNA lead to the production of more than one related protein, or isoform.

Autosomes: All of the chromosomes except for the sex chromosomes and the mitochondrial chromosome.

Centromere: The constricted region near the centre of a chromosome that has a critical role in cell division.

Codon: A three-base sequence of DNA or RNA that specifies a single amino acid.

Conservative mutation: A change in a DNA or RNA sequence that leads to the replacement of one amino acid with a biochemically similar one.

Epigenetic: A term describing non-mutational phenomena, such as methylation and histone modification that modify the expression of a gene.

Exon: A region of a gene that codes for a protein.

Frame-shift mutation: The addition or deletion of a number of DNA bases that is not a multiple of three, thus causing a shift in the reading frame of the gene. This shift leads to a change in the reading frame of all parts of the gene that are downstream from the mutation, often leading to a premature stop codon and ultimately, to a truncated protein.

Gain-of-function mutation: A mutation that produces a protein that takes on a new or enhanced function.

Genomics: The study of the functions and interactions of all the genes in the genome, including their interactions with environmental factors.

Genotype: A person's genetic makeup, as reflected by his or her DNA sequence.

Heterozygous: Having two different alleles at a specific autosomal (or X chromosome in a female) gene locus.

Homozygous: Having two identical alleles at a specific autosomal (or X chromosome in a female) gene locus.

Intron: A region of a gene that does not code for a protein.

Loss-of-function mutation: A mutation that decreases the production or function of a protein (or does both).

Missense mutation: Substitution of a single DNA base that results in a codon that specifies an alternative amino acid.

Monogenic: Caused by a mutation in a single gene.

Non-conservative mutation: A change in the DNA or RNA sequence that leads to the replacement of one amino acid with a very dissimilar one.

Nonsense mutation: Substitution of a single DNA base that results in a stop codon, thus leading to the truncation of a protein.

Penetrance: The likelihood that a person carrying a particular mutant gene will have an altered phenotype.

Phenotype: The clinical presentation or expression of a specific gene or genes, environmental factors, or both.

Point mutation: The substitution of a single DNA base in the normal DNA sequence.

Regulatory mutation: A mutation in a region of the genome that does not encode a protein but affects the expression of a gene.

Repeat sequence: A stretch of DNA bases that occurs in the genome in multiple identical or closely related copies.

Silent mutation: Substitution of a single DNA base that produces no change in the amino acid sequence of the encoded protein.

Single-nucleotide polymorphism (SNP): A common variant in the genome sequence; the human genome contains about 10 million SNPs.

Stop codon: A codon that leads to the termination of a protein rather than to the addition of an amino acid. The three stop codons are TGA, TAA, and TAG.

Transcription: Synthesis of RNA from, and under the direction of DNA

Translation: Conversion of RNA strands into proteins

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National Health Committee (NHC) and Executive

The National Health Committee (NHC) is an independent statutory body which provides advice to the New Zealand Minister of Health. It was reformed in 2011 to establish evaluation systems that would provide the New Zealand people and health sector with greater value for the money invested in health. The NHC Executive is the secretariat that supports the Committee. The NHC Executive's primary objective is to provide the Committee with sufficient information for them to prioritise interventions and make investment and disinvestment decisions. They do this through a variety of products including Prioritising Summaries, Technology Notes, EpiNotes, CostNotes, Rapid Reviews, and Health Technology Assessments which are chosen according to the nature of the decision required and time-frame within which decisions need to be made.

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