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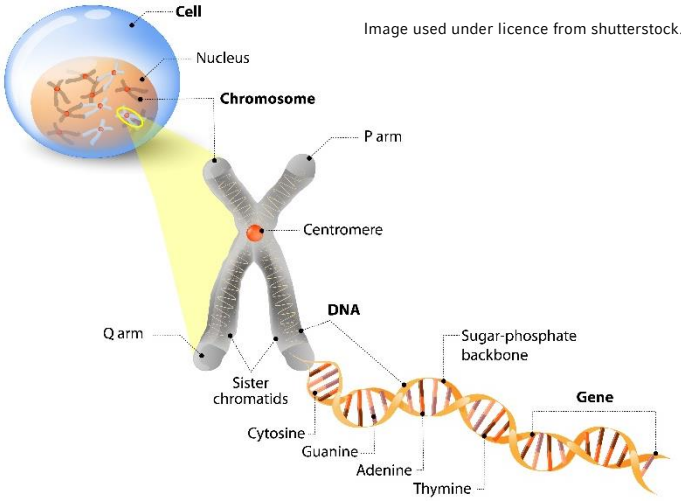
somewhat different

Learning to interpret the genome has essentially been the goal of scientists since the first human genome was sequenced.

Genetic tests: are they all equal?

Imagine what you could witness from looking inside the nucleus of just one of your cells. Each of the twenty-three pairs of chromosomes containing groupings of deoxyribonucleic acid (DNA) that make up our genes can be unwound, collectively resulting in two-metre long strands containing over three billion nucleobase pairs[1]. But what could you expect to learn from your entire sequence of base pairs, or even just the estimated 2% of your DNA that makes up your genes? Learning to interpret the genome has essentially been the goal of scientists since the first human genome was sequenced over fifteen years ago and, while significant strides have been made in this regard, the industry is still comparatively nascent.

This article discusses what a genetic test can reveal about us, the variety of genetic tests available and some of the pitfalls we can experience as underwriters, or indeed consumers, of these genetic tests.



The DNA molecule is a double helix. A gene is a length of DNA that codes for a specific protein.

Studying the genome

Two human genomes are 99.9% identical, but that means any two people differ at on average three million positions in their DNA. Each gene encodes proteins to make a tiny part of an organism; the sum of all instructions coming from roughly twenty-thousand genes comprise us. This helps to explain why we are so similar and yet individually unique. But how do we compare one another's similarities and differences beyond the manifest characteristic (phenotype)?

The first sequenced human genome formed the basis for the 'reference genome' still used today, albeit after multiple refinements[2]. The purpose of the reference genome is to enable us, among other things, to look at our evolution and development and to study human variation and disease.

A relatively simplistic description of a 'phenotype-first' approach to identifying nucleobase variants of significance is to frame it in terms of observational comparison. By comparing study genotypes against control genotypes, one can start to identify shared variants in the group with the

[1] See TOLEDO, C. & SALTSMAN, K., 2012

[2] See Genomics Education Programme, 2017

phenotype you are researching. By undertaking such 'genome-wide association studies' (GWAS), one can begin to identify which single nucleotide polymorphisms* (SNPs) are associated with a phenotype, to what degree, and whether the association is on a monogenic or polygenic level. GWAS are not without their limitations, but they are useful in helping us visualise how researchers can identify genetic causes of phenotypes.

Technological advances have dramatically reduced the costs of sequencing, hence resulting in a myriad of genetic tests coming to market. Indeed, as of August 2017 it was noted that there were over seventy-five thousand different genetic tests to choose from[3]. Tests range from diagnostic tests, to predictors of both disease and disease severity, to those that enable medication selection and dosage, to tests for the discovery of genetic factors that could be passed on to your children and for newborn screening, through to ancestry testing, 'health and wellness'-related screening or even tests that claim to match you with your preferred wines or partner.

Quick reference guide to some more common genetic test classifications

*Single nucleotide polymorphism (SNP) genotyping: SNPs are the most common type of genetic variation with millions occurring in each genome. SNPs occur when a single letter (nucleotide) of a person's genetic code is altered. Genotyping array technology enables the study of multiple SNPs an individual may carry and is usually the basis of direct-to-consumer (DTC) genetic testing. The measurement of genetic variation, specifically within single base pair mutations, aids in establishing the aetiology of many human diseases, response to drugs etc.

Hereditary cancer panels: Screening for genes based on risk potential in the development of certain cancers with hereditary susceptibility. Examples include breast, ovarian, colorectal and prostate cancers.

Cancer (somatic) sequencing: Sequencing of DNA unique to a tumour, typically to identify targeted therapies. This technique allows for highly accurate resolution of tumour-causing mutations.

Whole genome sequencing: Sequencing of the entire human genome, to include protein coding regions and non-coding regions (which may be involved in gene regulation) for the purpose of predictive and precision medicine.

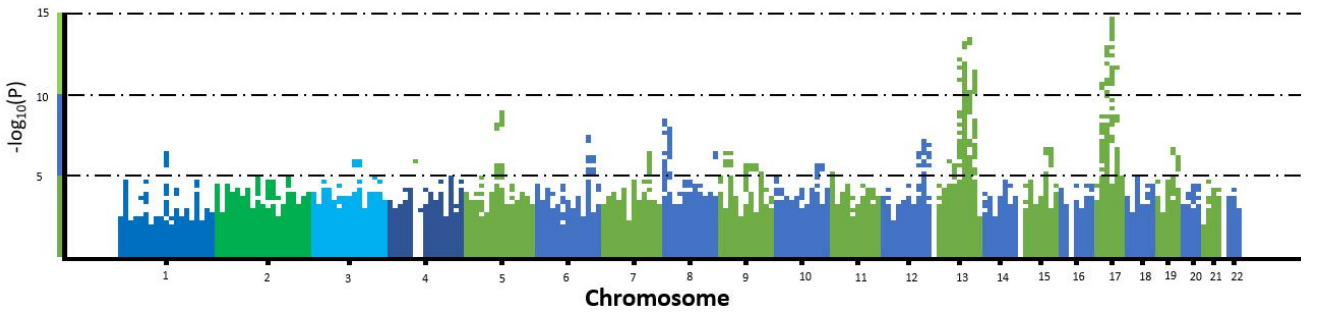
Whole exome sequencing: Sequencing all of the protein coding regions of the genome, allowing identification of genetic variants that may alter protein sequences and therefore protein function.

Pharmacogenomics: Study of how the genetic make-up of an individual affects his/her response to drugs.

Nutrigenomics/'health and wellness': Study of both the effects of food constituents on gene expression and the response of individuals to nutrients based on their unique genome.

Epigenetics: The study of the biological mechanism that regulates gene expression, but does not alter an individual's genetic code.

GWAS illustration showing SNPs, including phenotype association (Y-axis) and their location by chromosome
SNPs present on chromosomes 13 and 17 appear strongly associated with the study phenotype, breast cancer



[3] See RAPAPORT, L. Reuters, 2018

Most genetic tests on the market fall into one of the above classifications. Many will require physician initiation, but increasingly providers are marketing directly to the consumer (DTC) – a development not without some controversy[4] owing primarily to counselling, privacy and ongoing care reasons.

This is of course all rather complex and, notwithstanding regulatory restrictions, how should we as insurers evaluate these test results? As with any test we need to be confident that the result is reproducible and reliable, counting on these three criteria to do so: analytical validity, clinical validity, and clinical utility. To put it another way, if I send a sample to three different laboratories, will I get the same result back, will the result provide prognostic value and is it actionable?

A case study

To illustrate where one can receive a result that does not perhaps meet all three criteria, consider breast cancer, well known for having a genetic component through mutations in the BRCA1 and BRCA2 genes. In fact, there are over two thousand variants across BRCA1 and BRCA2 genes known to have pathological significance for breast, ovarian and other cancers[5], although not all BRCA gene mutations are as notable as others[6]. Additionally, researchers have recently identified seventy-two variants across genes other than BRCA1 and BRCA2 that are also associated with a higher risk of breast cancer[7].

Note that some well-known DTC genetic tests only test for three of the so-called 'founder variants', BRCA1 5382insC insertion and BRCA1 185delAG, BRCA2 6174delT deletions.

With this in mind, consider a strong family history of breast cancer that may warrant adverse terms for insurance purposes. Would you, as an underwriter or an individual, be fully satisfied that a genetic test confirming no mutations of the above three selected variants proves no increased risk of breast cancer based on genetic predisposition? As an individual, would you want further reassurance? And as an underwriter, leaving aside regulatory or philosophical considerations around giving credit to negative genetic test results, would you still rate the policy?

There is the potential that reassurance taken from negative DTC tests for BRCA gene variants could be comparable to a 'false negative' if the consumer is unknowingly positive for a non-tested pathological variant. Further complications surrounding the reliability of results are illustrated by a study highlighting that as many as 40% of DTC test variant results returned false positives[8], perhaps underpinning how essential clinical confirmation testing is in this developing field.

We are well aware as underwriters of how important it is to be cognizant of the sensitivity and specificity of tests; however, not only is this information not readily available in this largely unregulated and rapidly evolving market, most disease is not perfectly predictable with so many environmental and lifestyle factors also playing their part in gene expression.

> Genes load the gun, your environment pulls the trigger[9]
> Francis Collins

Scientists recognise that the science of systems biology is multi-disciplinary with advances in sequencing technology giving rise to complementary 'omics' such as epigenomics, transcriptomics, microbiomics and so forth. Francis Bacon philosophised in the early seventeenth century that his empirical theory of scientific principle would "eventually disclose and bring into sight all that is most hidden and secret in the universe"[10]; perhaps, with the sheer volume of data we are starting to generate about ourselves, diseases, and our environment, we may come much closer to fulfilling his prediction.

Conclusion

On balance, I take the view that the democratisation of genetic testing will prove positive for humanity as it will undoubtedly aid drug discovery, empower patients and move us closer to preventative rather than curative medicine. The blurring of the boundary between physician- and patient-initiated tests needs careful consideration by government, health services, genetic testing companies and consumers and of course poses a threat to us, as insurers, given the scope for information asymmetry. There is a wide

[4] See HUNTER, DJ et al., 2008
[5] See The University of Utah, BRCA Mutation Database
[6] See REBBECK, TR et al., 2015
[7] See Breastcancer.org, 2017
[8] See TANDY-CONNOR, S. et al., 2018
[9] See KRESSER, C., 2016
[10] See Biography.com

variety of genetic tests, ranging from whole genome sequencing through to tests initiated for non-medical purposes. Nevertheless, while genomics is rapidly becoming more prevalent for diagnostic and research purposes, scientists recognise that we will not find all the answers in our genome. Just as one piece of medical evidence may only provide us with part of the picture when we are underwriting, genomics is just one piece of the jigsaw in a multi-disciplinary, 'multi-omics' approach to disease[11].

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Contact

Gareth Matthews
Chief Underwriter
Tel. +353 1 633-8869
gareth.matthews@hannover-re.com

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[11] See HASIN, Y et al., 2017