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A Study Into The Impact Of Preprogrammed Genetic Health Risks In Retirement Planning

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Synopsis

A brief synopsis of items covered in this paper is given below The narrative is in the same order as far as possible.

1. Human life expectancy and prognosis of health conditions is possible based upon the genetic profile of people which is the actual identity of who one is.
2. With the developments in genetic research, it is possible to reasonably identify preprogrammed health risk depending on a person's DNA. While this is 100 percent possible in the cases of diseases like Huntington's, in some other cases, fully developed tests are still in progress though a reasonable estimate is feasible now.
3. It can be reasonably identified how long might a person be expected to live based upon the DNA study through Genetic Scores, Disease Association Analysis, Polygenic Score Analysis and other methodologies. Polygenic disorders, involving multiple parameters and multifactorial influences makes the need of huge data imperative and for their analysis there is need for Big Data and Artificial Intelligence to be used.
4. Impact of family history with respect to health and longevity of relatives on longevity of persons is there and possible to be identified. With proper analysis it is possible to study the effect of relatives' health and heredity on the individuals.
5. There is need to have a framework of regulations to handle the situations arising from these developments. It would be advisable to have well defined regulatory frameworks in place so that all the stakeholders, viz. the customers, insurance industry, other institutions like the medical fraternity and overall society stand to benefit. The present situation is that there are three distinct groups of countries based on the stringency of regulations they enforce. A broad convergence of regulatory approach is desirable and may be expected in the future.

Executive Summary

The phenomenon of population aging has become a major concern for policy makers globally. Longevity is increasing at different rates across different countries, different age groups and between males and females. Longevity increases at older ages have been more prevalent for developed countries whereas longevity increases at birth have been prevalent for developing countries. In addition to this, genetic research has been on the rise globally. Genetic testing and the consumer wellness genomics market is anticipated to reach USD$4.6 billion by 2025. The most famous example one could readily recall for this is Angelina Jolie who underwent a double mastectomy after discovering that she has a gene mutation BRCA1 which, in addition to BRCA2 or alone, markedly raises her risk of breast and uterine cancer. With the advancement in the field of genetic testing over the last decade, several thousands of genetic variants have been discovered including the greater risk they confer for various diseases like Cancer, Parkinson's, Alzheimer's, Celiac disease and others.

Recent cutting-edge research also creates a distinct understanding that humans are preprogrammed in their DNA to develop certain diseases depending on and owing to the DNA mutations and targeted treatment based upon identification of such mutations also holds promise. For example, it is now recognised that all humans are preprogrammed to innate carcinogenesis through the co-occurrence of metastases caused by Quantum Entanglement Entropy which is basically a process providing a mechanistic explanation between causal factors and associated health and longevity of individuals[1]. For example, in the human context, Heterochromatin Protein (HP1) acts as the epigenetic marker for colon cancer and CRISPR-Cas9 enzymes act sort of like molecular scissors or genetic scalpels, snipping away pieces of defective genetic code and swap them with a replacement. The innate immune system functions as an interpreter of tissue damage and provide a first line of defense, translates the information to other repair and defense systems in the body by stimulating angiogenesis, wound repair and activate adaptive immunity with autophagy being a means for programmed cell survival balancing and counter-regulating apoptosis. For colon cancer, it is now quite well understood as to how cells replicate in cancer patients and how to put a stop to the process, including how to reverse a tumor through the regulation of cell-to-cell adhesion and miRNA (microRNA) biology. This kind of preprogrammed propensity to diseases based on DNA mutation is not unique to colon cancer alone but is discovered to apply to other cancers also and could apply to many other diseases in general that could need more focused research to be established.

Further, the study of the human genome facilitates identification of inherited genetic variants that increase or decrease the risk of complex diseases and development of new methods for genotyping individual DNA samples at 500,000 or more loci have led to a wave of discoveries through Genome Wide Association Studies (GWAS). For example, Apolipoprotein E (APOE), found as three isoforms, APOE2, APOE3 and APOE4, which is the only gene with common variants that have consistently been associated with longevity, has an important role in regulating lipoproteins and is associated with cardiovascular risk and Alzheimer's. Similarly, the -641C allele in the APOC3 promoter is present at a higher frequency in centenarians and their offspring compared with controls[2].

Lot of evidence links aging to genetic and epigenetic alterations and with the reversible nature of epigenetic mechanisms, they provide promising avenues for prediction and interventions against age-related decline and disease. For example, manipulations of more than 100 genes have been found to increase longevity in C'elegans and generalities from studies of lifespan-increasing invertebrate genes is understood and some of it replicated in few higher life forms. For example, DNA methylation age of blood can predict all-cause mortality in later life and studies have identified biomarkers of chronological age based on DNA methylation levels.

Of all the methods now known, epigenetics offers the most promise in old age management through the medium of:

1. Gene control: Epigenetics determines cell specialization and, through environmental stimuli, can cause genes to be turned on or off.
2. Universality: Such things as diet, lifestyle, sleep pattern, and exercise can lead to modifications around genes to turn them on or off to predict cancer, Alzheimer's and other diseases.
3. Inheritance: Enables us to understand ourselves and indications are some epigenetic changes can be inherited.
4. Reversibility: With over 20,000 genes, we could theoretically address most old age issues viz. control cancer, slow aging, stop obesity etc.

As per epigenetics, aging is characterized by

(i) Loss of histones leading to altered tissue functions and decline in fitness;

(ii) Imbalance of activating and repressive modifications leading to loss of cell integrity;

(iii) Transcriptional changes of DNA and Proteins;

(iv) Losses and gains in heterochromatin causing sterility and promoting aging;

(v) Breakdown of nuclear lamina causing cell senescence;

(vi) Global hypomethylation and focal hypermethylation; and

(vii) Chromatin remodelling: loss in chromatin remodelling which causes genome instability.

The epigenetic changes are heavily dictated by environmental stimuli and nutrient availability that in turn alter intracellular metabolite concentrations. Indeed, genetically tractable models have been used to investigate both replicative lifespan and chronological lifespan, though there is still scope for these to be carried out in more detail in humans. If we consider the combination of DNA methylation & histone modification patterns, with the possibility of paramutation, it would be very likely possible for epigenetics to be a significant contributor to unravel the complexity of the genetics of common diseases.

It is also noticed that the genetic traits, as the name suggests, run in families and it is realized that heritability estimates for obesity are high at ($p > \sim 0.70$), comparing well with other complex, polygenic diseases such as schizophrenia ($> \sim 0.81$) and autism ($> \sim 0.90$) and are significantly higher than for other complex traits such as hypertension ($> \sim 0.29$) and depression ($> \sim 0.50$)[13]. It is also established that DNA methylation-derived measures of accelerated aging are heritable traits and methylation age acceleration predicts mortality which means that it can be used to predict mortality independently of health status, lifestyle factors and known genetic factors[12]. Thus, family history with respect to genetics also play a very important role regarding individual health and therefore their study is quite important for informed decision making.

It will be helpful for policy makers to understand the impact to better plan for the future and harness its benefits for societal good. Therefore, the purpose of the present paper is:

1. To identify preprogrammed health risk depending on a person's DNA
2. If, based upon the DNA, it can be identified how long might a person be expected to live
3. Impact of family history with respect to health and longevity of relatives on longevity of persons
4. Have a framework of regulations to handle the situations arising from these developments

We explore some ideas as to how we can think use the above for retirement or old age planning. The learning from this paper should contribute to the industry and society by identifying the impact such prognosis could provide and empower the stakeholders and regulators to better design interventions and strategies for improved old age and improved retirement planning.

Section 1: Methodology of Research and the Materials Used

For this paper due reference has been made to the medical journals, websites of research institutions, insurers, regulators, census reports and government departments as mentioned in the Endnotes section.

The main aim is to isolate the impact and potential promise, of developments in genetics and epigenetics testing vis-à-vis the insurance and financial industries with respect to planning for retirement and advanced ages. In addition, experience related information from the industry sources viz the government medical institutions and departments available to public, learnings of Longitudinal Aging Study in India (LASI), Singapore Longitudinal Ageing Studies (SLAS), Institute of Actuaries of India, Actuarial Society of Singapore and information about centenarians in Singapore from the Ministry of Health, Singapore. All necessary data will be masked to ensure data protection.

Section 2: Methodology of Research and the Materials Used

Recent research indicates that the role of DNA is much wider than the way one resembles their family members and can be a predictive tool. With respect to genetic theory of aging, the genes and their mutations in those genes are responsible for how long one could live. At the same time, we know that genetics alone are not the sole cause for aging for which there are many more causes. Various diseases and conditions related to heritable gene mutations can directly impact lifespan like cystic fibrosis, sickle cell anemia, Tay-Sachs and Huntington's disease. Some genes or their mutations could be harmful or beneficial and affect longevity. For example, the gene that helps a person metabolize cholesterol would reduce a person's risk of heart disease; the sickle cell mutation that causes anemia also confers enhanced protection against malaria and some other mosquito vector borne diseases. Some of the major theories in this subject are explained below:

1. *Theories of Aging* that briefly describe the purpose of aging:
    a. An accumulation of damage and wear and tear to the body eventually leading to death through:
        (i) Wear and tear theory of aging
        (ii) Rate of living theory of aging
        (iii) Protein cross-linking theory of aging
        (iv) Free radical theory of aging
        (v) Somatic mutation theory of aging
    b. Programmed longevity viz. an intentional process controlled such that it is like other phases of life. This can be through:
        (i) Programmed longevity - Programmed longevity claims that life is determined by a sequential turning on and off, of genes that happens as a natural process.
        (ii) Endocrine theory of aging
        (iii) Immunological theory of aging

c. *Telomere lengths* control the number of possible cell divisions. Generally, cells can divide about 50 times (Hayflick limit). Cancer cells have evolved to not remove but sometimes add to telomere length and some cells like white blood cells do not undergo telomere shortening. Seemingly while genes in all cells have the code word for enzyme telomerase which inhibits telomere shortening, it is only "expressed" in cells like white blood cells and cancer cells. Scientists theorize that if telomerase could be activated in other cells, but controlled, our longevity could be extended, and this angle needs more study. Studies show that some chronic conditions like high blood pressure are associated with less telomerase activity while healthy diet and exercise are linked with longer telomeres.

d. *Longevity genes* are specific genes associated with living longer, for example SIRT1 and SIRT2 (Sirtuin 1 to SIRT7 in mammals) polymorphisms are associated in several disease related phenotypes, including diabetes, body mass index, obesity, cholesterol metabolism, energy expenditure, glucose tolerance, and cardiovascular disease.

e. *Stem cells* - these are immature cells which can potentially become many types of cell which can be used to further longevity as stem cells are only a small number of the cells present in the body.

f. *Epigenetics* - refers to gene expression viz. understand how genes turn on or off and how environmental factors may work within the constraints of genetics to protect or predispose to disease.

It is estimated that genes can explain about 35 percent[8] of lifespan, which is quite significant, but leaves a big portion unexplained also. Aging is a multifactorial process and multiple approaches are needed including human behavior, exposures and random chance.

So, it must be recognized that genetics-based prediction of disease traits, while possible is still quite difficult. Recent technological advances in high-throughput genotyping, RNA expression, and massively parallel sequencing have accelerated interrogation of genetic variation for understanding human disease and drug response. It is well known that variation in disease course, severity, and response to medication is reflective of the underlying individual allelic repertoire, offering the opportunity for genetics to facilitate early treatment, preventative medicine, preemptive selection of efficacious drugs, and more accurate estimation. Towards this end we basically need the following:

(1) Get a brief overview of the current state of human disease mapping as this provides the foundational knowledge for genetic-based disease prediction.

(2) Describe the process of disease prediction in a simple probabilistic framework detailing the general qualities of clinically useful predictive models and also detailed examples.

(3) Provide an overview of the basic classes of genetic-based prediction models and measures of prognostic utility.

(4) Illustrate the application of genetic-based predictive models to data from biobanks and prospective cohorts.

While the use of genetic results in pharmaceutical development is its primary purpose, the equally promising use would be the accurate prognosis of diseases, ascertaining all-cause mortality and finally use for financial

planning. The utility of predictive models is derived primarily from the correlation patterns they can generate provided that these are robust across intended populations. However, the strength and robustness of the correlation are critical for a genetic prediction model to be useful. Predictive models are most beneficial when they yield actionable and individualized results for a majority of the population. So, the ideal genetic-based predictive model for clinical applications should:

1. Substantially modify the posterior probability of medical traits vis-à-vis existing clinical assessment.
2. Impact majority of individuals and provide improved outcomes.
3. Allow broad applicability that defines an archetypal genetic-based predictive model.

To develop such predictive models, GWAS results are useful provided the posterior probabilities approach 1 or 0 since a majority of individuals have mostly intermediate posterior probabilities. So, it is very useful to have genetic information to further modify posterior probabilities for those individuals thought to be of intermediate risk. Disease prediction using genetic testing has diverse applications, in treatment, prognosis and possibly mortality prediction also by extension. This is aided by using single nucleotide polymorphisms (SNPs) that are disease-susceptibility markers and help to identify propensity to diseases, the diseases course, severity, and possible response to medication. But it must be recognized that the accuracy depends upon how correctly the diseases genetic component of etiologies are identified. Unfortunately, the discovery of individual disease etiology is not uniform across all major diseases. For example, while it is well identified in diseases like cancer or diabetes, in some other diseases it is still in infancy. And it must also be noted that for polygenic etiologies, methods must be used to combine signals from multiple genetic markers together into a cohesive metric for prediction, multicollinearity between markers addressed and identify principal component regression. Another concern is marker-marker interactions. Since interaction analysis is computationally intensive, larger sample sizes are typically needed to detect interaction effects than are needed to detect main effects.

Use of regression methods for prediction modelling is promising to estimate the ratio of probability of genotype information given disease to probability of genotype information within non-diseased population and incorporating covariates and interaction is possible provided the results are to measure the uncertainty of the risk estimates and not necessarily point estimates alone. While multicollinearity between markers is a concern, principal component regression is useful along with dropping or imputing samples with missing data. For presence vs. absence of disease phenotypes, a predictive model is first developed by analyzing a case-control dataset, and then applied to a population.

To compute confidence intervals for risk estimates from a meta-analysis, each individual study should do a joint analysis and return coefficient estimates and the variance-covariance matrix for the coefficients. Then this can be combined to estimate the overall variance-covariance matrix and a precise confidence interval for the risk estimates.

Use of Bayesian networks has promise to obtain posterior probabilities. Once genetic markers in the Bayesian Network can be reasonably modeled as being conditionally independent, then the network can be reduced to a naive Bayes model and with n genetic markers. Using Bayes' rule one can write the posterior probability of the disease trait (PPD)[9], as:

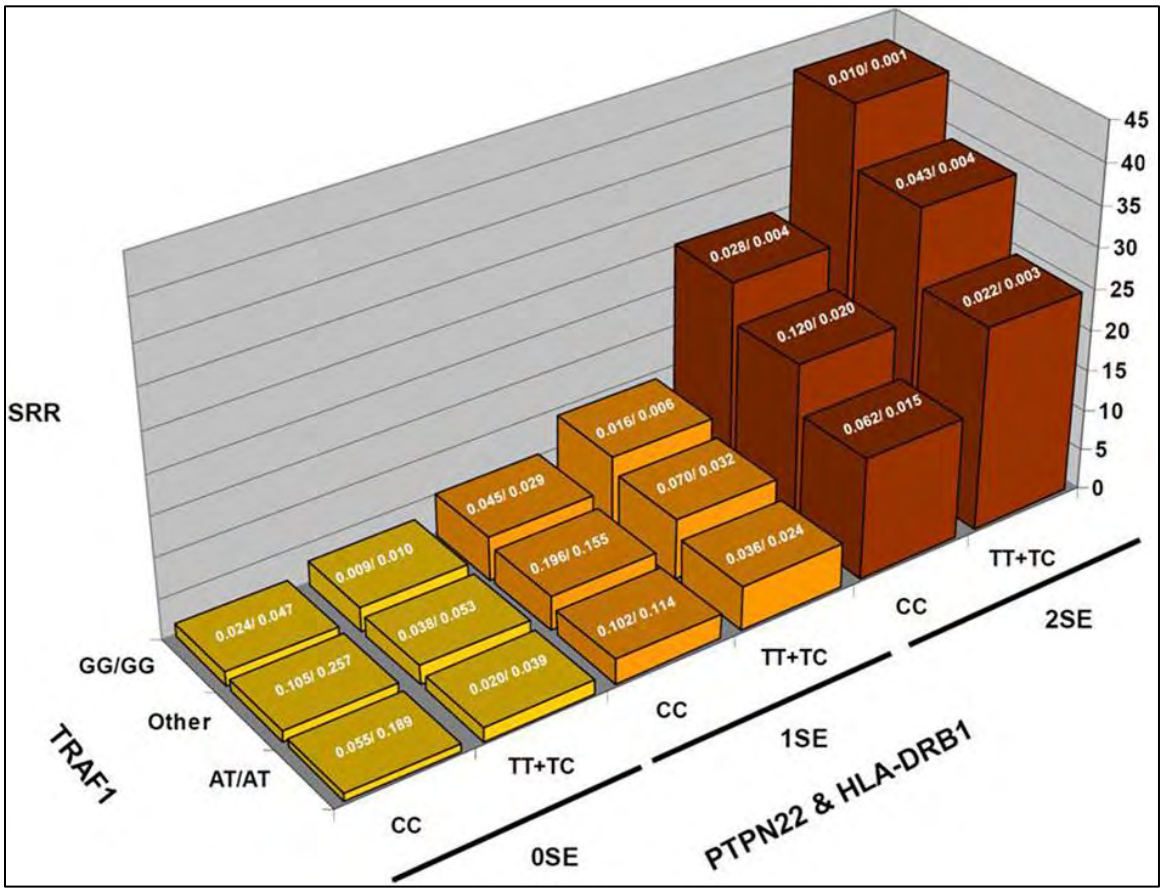
$$PPD^{n}=P(D||\cap^{ni}=1G^{i})=P(\cap^{ni}=1G^{i}|D)P(D) / P(\cap^{ni}=1G^{i})$$

where D denotes a random variable for the disease trait and n genetic markers are used in the prediction. Under the conditional independence assumption of naive Bayes, we can completely factorize the product and, for a binary trait (D = 1 to denote disease and D = 0 for non-disease), the PPD is:

$PPD^n = P(D=1)\prod^{ni=1}P(G^i|D=1)P(D=1)\prod^{ni}=1P(G^i|D=1) + P(D=0)\prod^{ni}=1P(G^i|D=0).$

Figure 1

RHEUMATOID ARTHRITIS SCALED POSTERIOR PROBABILITIES (SRR) BASED ON GENOTYPE HLA-DRB1, TRAF1, AND PTPN22



Source: Genetic-based prediction of disease traits of Steven J Schrodi et al

Prognosis of disease traits with genetic information are classical problems of classification and clustering within machine learning. Hence, numerous machine learning methods, such as neural networks, support vector machines, and random forests can be applied to these types of data sets. Currently, the use of these methods to address problems using gene expression is arguably more advanced than the analogous methods applied to DNA variation data. Many complex diseases are themselves the outcome of processes. For example, many forms of heart disease arise through cumulative changes such as raised blood pressure, raised cholesterol or onset of diabetes, as well as environmental factors such as smoking. Genes that affect the underlying processes may have an effect much less dramatic than if they affected the disease endpoint directly.

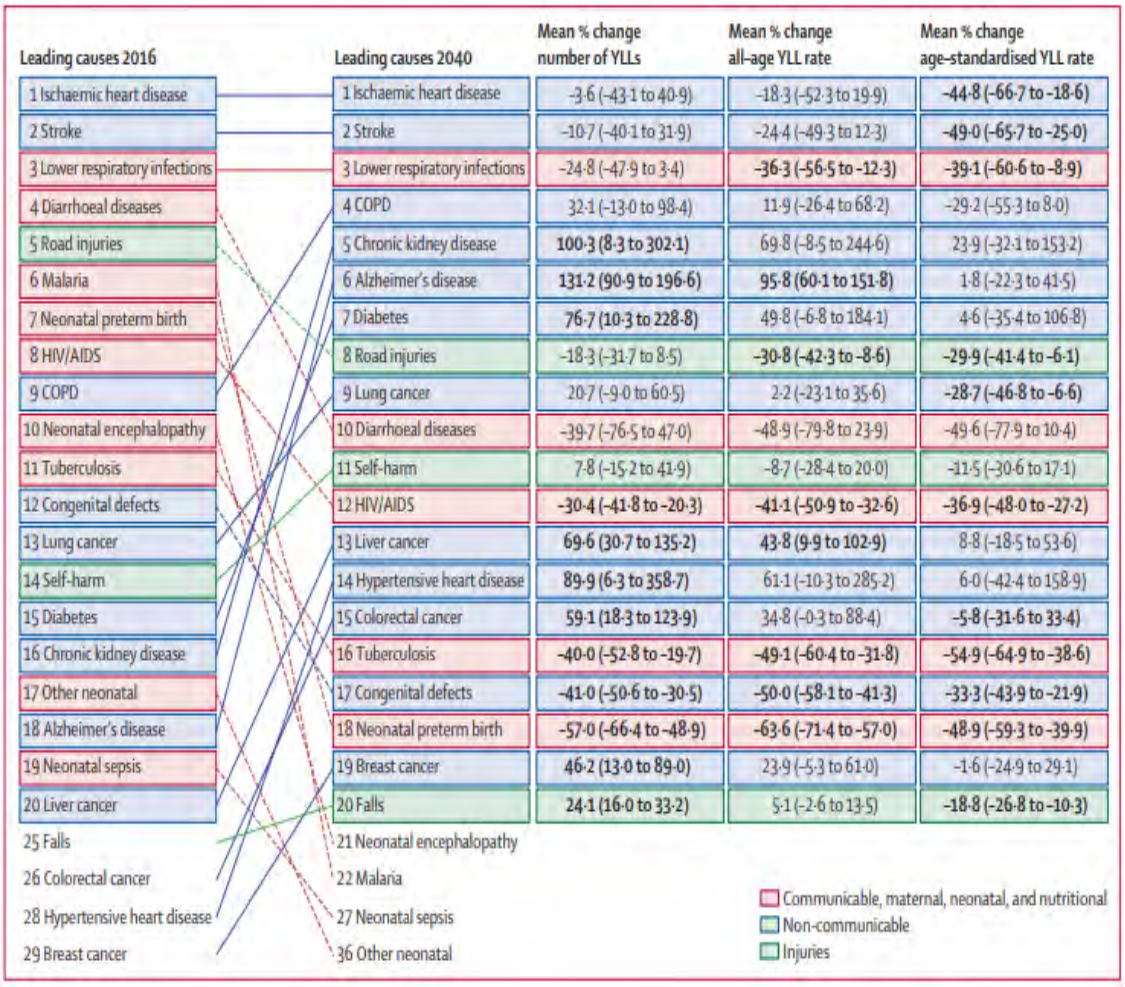
However, the need of large computational power to crunch the huge amounts of data is very much there in the current stage. As mentioned earlier machine learning and Artificial Intelligence (AI) would be needed extensively to do this efficiently. New AI technology can identify genetic disorders not only from data but also through external data such as a photo of a patient's face through algorithms that are identified to be even better than clinicians at accurately identifying genetic syndromes with recognizable facial features with

an astounding accuracy rate of 96.88 percent for Cornelia de Lange Syndrome and even Down's Syndrome. Similarly, AI to interpret chest X-ray images to diagnose more than a dozen medical conditions exist.

Since the number of diseases people may experience is huge and constraints in terms of time, budget, resources etc. exist, it may not be possible to study the effect of each and every combination of gene mutation. A prioritization of important diseases expected to be followed in the future would be better in terms of utility and productivity. For example, the figure below shows the present leading causes of deaths and also years of life lost (YLL) and how it could change in the future. If the research is focused on these specific group of diseases to begin with, the benefits would be forthcoming faster.

Figure 2

LEADING 20 LEVEL 3 CAUSES OF YLLS GLOBALLY IN 2016 AND 2040 BY RANK ORDER



Source: Lancet

2.1 ANALYSIS OF INDIVIDUALS DNA

Most diseases are linked not to one mutation, but rather to thousands of mutations each with a small effect, about 1 percent, on a person's odds of getting a disease[12]. So, it would not be fully useful to test in isolation. But it is possible to combine data on all DNA changes to construct an individual risk score to calculate their

significance. Genetic research has determined that all humans, no matter the geographic origin, are about 99.5 percent the same genetically. Studies of twins have shown that approximately 25 percent to 50 percent of morbidity and mortality differences from person to person are due to genetic variation[12]. The remaining variation in disease rates are due to environmental, behavioral, and lifestyle factors[14].

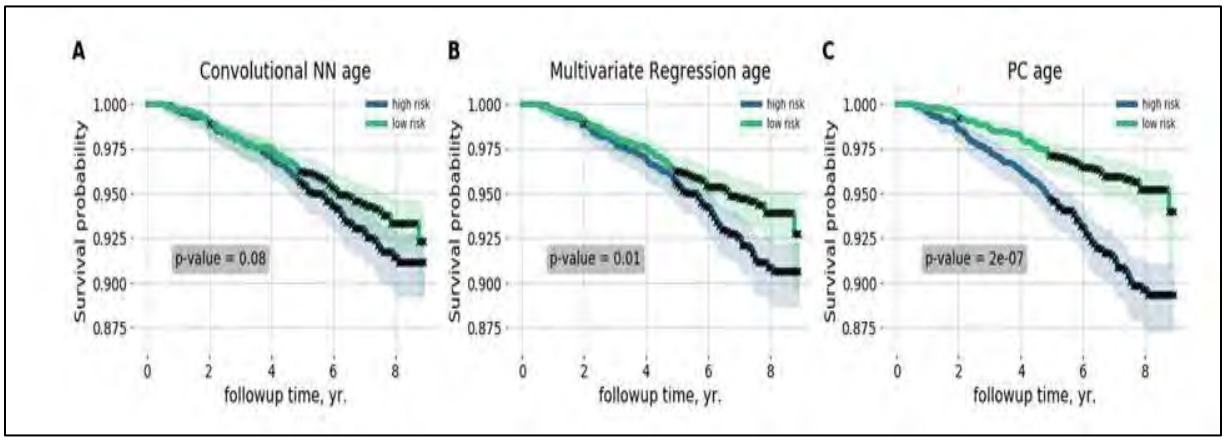
Predictive Tests for conditions like heart disease, diabetes have been developed to screen multiple genes implicated in common diseases for personalized risk scores. By examining DNA changes at over 6.6 million places in a human genome, we can identify a greater portion of the population at risk for enhanced screening and therapies. But DNA is essentially alterable, and a healthy lifestyle and medications can reduce risks.

DNA analysis for risk prediction could be through risk scores or regression analysis. Risk scores method is like a numerical rating method of underwriting which constructs the predictive model based on the sum of predisposing genotypes that each individual carries, unweighted or weighted by the effect size of specific predisposing genotypes. The basic approach is to take a weighted sum of risk alleles and choose risk alleles based on those found to be genome-wide significant in a recent meta-analysis. Weights are determined for each risk allele through β estimates from meta-analyzed GWAS. Unweighted Genetic Risk Scores (GRS) treat each risk locus equally. To illustrate the weighted GRS approach, assume that *k* SNPs are known to be genome-wide significant and further assume that the corresponding β weights from the GWAS are denoted as w_i for the i^{th} SNP.

With respect to individual mortality, biological age perhaps is more important than chronological age as patients diagnosed with diabetes or hypertension are biologically older than healthy peers and the difference translates into a lifespan change. This point comes out in the study of National Health and Nutrition Examination Survey (NHANES) death register with survival (3750 male, 4087 female, aged 18–85, follow-up time up to 9years, 701 participants died)[16]. The summary of Kaplan-Meier survival curves for NHANES participants, stratified into the high- and the low- risk groups according to the difference between the estimated biological age of an individual and the averaged estimated age of gender- and age-matched peers, gives a clear understanding of the differences.

(A), the multivariate regression, Regression Age (B), and the unsupervised PCA_Age (C) models. The p-values characterize the survival curves separation significance

Figure 3
SURVIVAL PROBABILITY PER METHOD



Source: Nature.com

Similarly, kriging concept can also be used in predicting genotypes and phenotypes and overall genetic values which is an important step in predicting individual mortality values. For humans, the interest is in predicting phenotypes for simple or complex traits either applied for genetic counseling by predicting the risk of genetic disorders with known mono- or oligogenic modes of inheritance and a certain history of cases in a known family structure, but accurate predictions of genetic predispositions to human diseases should also be useful for preventive and personalized medicine. The kriging approach consists of:

1. Estimation of unknown parameters and hidden variables by maximum likelihood or restricted maximum likelihood.
2. Prediction of the values of the regionalized variables by performing a best linear unbiased prediction, under the auxiliary assumption that the parameter values and hidden variables estimated in the first step are the true ones.

If the study group has q individuals with family history information, n of them being genotyped and having phenotype measurements of a certain quantitative trait, the overall model could be:

$y_i = w^T_i\beta + z^T_i u + g(x_i) + e_i$ for i =1 to n

with y_i as a measurement of the phenotype for individual i, β is a function of nuisance location parameter not of immediate interest but useful later, x_i is a p-vector of dummy SNP instance variates (genotype) observed on individual i, and g is a random function as a Gaussian random field. In matrix notation, the statistical model reduces to: $y = W\beta + Zu + g(x) + e$.

Needless to say, a single method may not always be adequate, and a combination of methods would be needed to address the needs.

2.2 IMPACT OF FAMILY HISTORY AND DNA ANALYSIS OF RELATIVES WITH RESPECT TO HEALTH AND LONGEVITY OF INDIVIDUALS

It is known that while we can reduce our risk of disease with healthy diet, exercise and not smoking, our family history is one of the strongest influences on risk of developing several ailments like heart disease, stroke, diabetes, or cancer. A study of personal predisposition versus family history is important since personal habits can carry much more importance than family history alone in deciding a person's longevity.

While we cannot change our genetic makeup, knowing the family history can help to identify any inherent risks and also plan to reduce risk of developing health problems. Family members share their genes, environment, lifestyles and possibly habits. Risks for diseases like asthma, diabetes, cancer and heart disease also run in families. With respect to family history, the primary factor of DNA is that it:

1) is unique to everyone
2) has predictive powers
3) may affect relatives
4) may be used to discriminate
5) emotionally affects persons

Historically, the discovery of the gene mutation for Huntington's Disease increased focus on genetic testing as it is 100 percent predictive being monogenic. In other cases, this distinction is not very conclusive and though a clear correlation is found, predictability is relatively less now. With the Human Genome Project and mapping the human genome sequence, we have a source book for insight into the possible treatment of approximately 7,000 rare genetic diseases that currently affect mankind. Key red flags in family history that may increase risk are diseases:

1) occurring at an earlier age than expected (10 to 20 years before most people get the disease)
2) in more than one close relative
3) that do not usually affect a certain gender (for example, breast cancer in a male) and
4) occurring in certain combinations within a family (for example, breast and ovarian cancer, or heart disease and diabetes)

If a family has one or more adverse or even positive features, it holds important clues about risk. People with a family history of disease gain the most from lifestyle changes and screening tests. One cannot change their genes but can certainly change unhealthy behaviors. Adopting a healthier lifestyle can reduce one's risk for hereditary diseases. Screening tests can detect diseases like cancer early and detect disease risk factors like high blood pressure which can be treated earlier thus keeping them in control and mitigating future complications. Most important data could include:

1) Major medical conditions and causes of death
2) Age of disease onset and age at death
3) Ethnic background

Various approaches to analyze the polygenic effect of family history on the prediction accuracy can be devised, for example the polygenic effect "α" (or a polygenic score) of a child can be calculated as:

$½ * (\alpha_{Father} + \alpha_{Mother}) + m$, where m is its Mendelian sampling term drawn from a normal distribution n from a normal distribution N (0; 0:25*(2-(F_{mother} + F_{father}))*σ^2_{poly}) with F_{mother} and F_{father} being the inbreeding coefficients of the corresponding mother and father.

Table 1

CUMULATIVE PROBABILITY OF BREAST CANCER FOR A WOMAN WHO HAS A RELATIVE WITH BREAST CANCER BY AGE OF ONSET

	Age of onset in affected relative					
Age of Woman	**20-29**	**30-39**	**40-49**	**50-59**	**60-69**	**70-79**
29	0.70%	0.50%	0.30%	0.20%	0.20%	0.10%
39	2.50%	1.70%	1.20%	0.80%	0.60%	0.50%
49	6.20%	4.40%	3.20%	2.30%	1.80%	1.50%
59	11.60%	8.60%	6.40%	4.90%	4.00%	3.50%
69	17.10%	13.00%	10.10%	8.20%	7.00%	6.20%
79	21.10%	16.50%	13.20%	11.00%	9.60%	8.80%

Credit or permission line goes here.

Table 2

μ-RATIOS C WITH FAMILY HISTORY OF BC/OC/BRCA MUTATION, 30-YEAR-OLD WOMAN AT ONSET FOR BREAST CANCER

Age	**1 FDR-BC**	**1 SDR-BC**	**2 FDR-BC**	**1 SDR-OC**	**BRCA**
31	1.0000	1.0000	1.0000	1.0302	1.0298
33	1.0345	1.0161	1.1051	1.1946	1.3543
35	1.0999	1.0465	1.3034	1.4011	1.8615
37	1.1822	1.0848	1.5518	1.5958	2.4323
39	1.2627	1.1225	1.7927	1.7350	2.9322
41	1.3385	1.1580	2.0519	1.7070	3.2351
43	1.3004	1.1391	1.9045	1.5812	2.9300
45	1.2927	1.1358	1.8999	1.6926	3.0133
47	1.3026	1.1362	1.9167	1.8143	3.1367
49	1.3174	1.1414	1.9586	1.9083	3.2691

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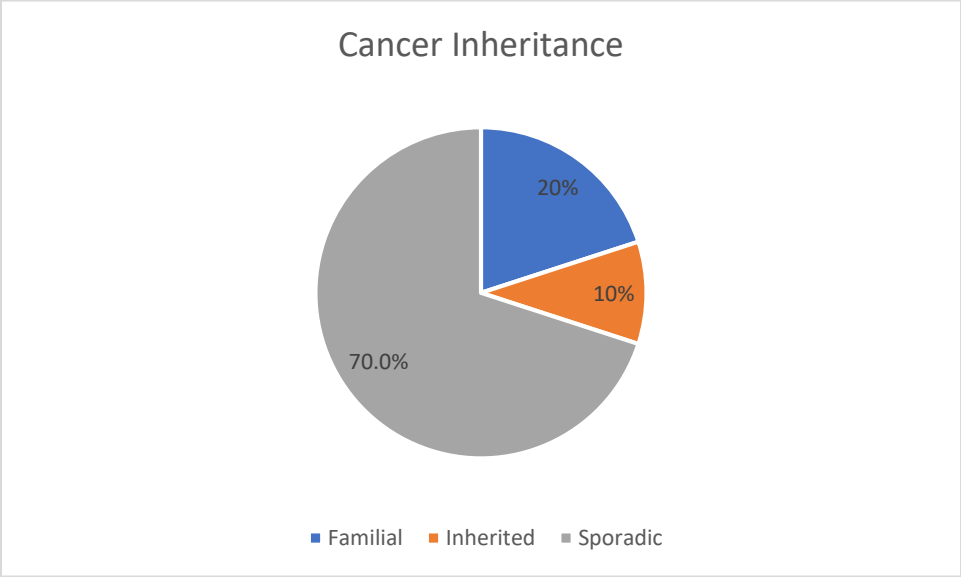
As per the study by the National Cancer Centre Singapore[20], over 400 hereditary cancer susceptibility syndromes have been described, most of which feature an autosomal dominant inheritance pattern. Although many of these are rare syndromes, they account for at least 5–10 percent of all cancer incidences.

Figure 4
INHERITABILITY EXPERIENCE OF CANCER IN SINGAPORE



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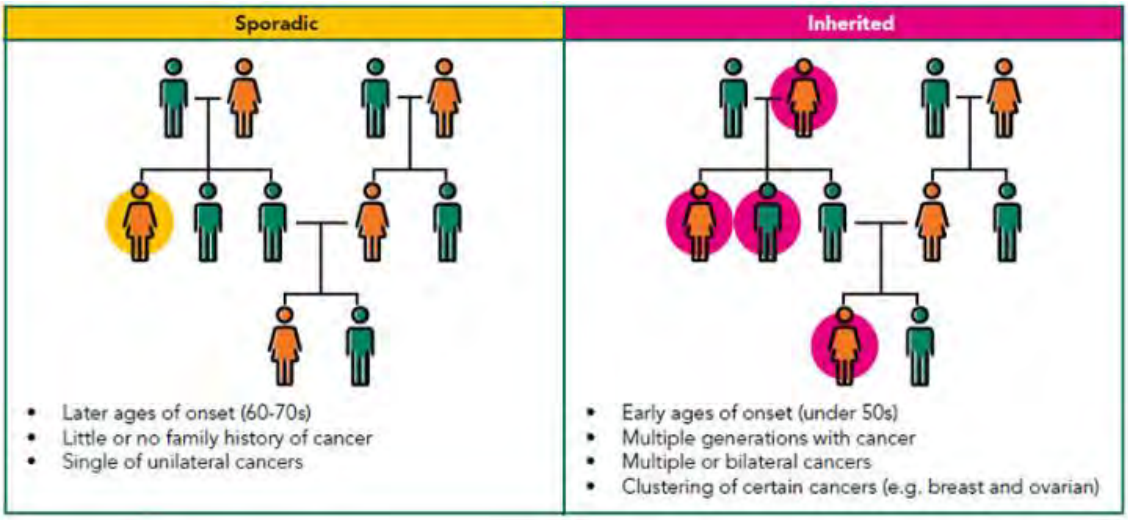
On further study, an inherited cancer susceptibility syndrome is usually suspected in families with the following characteristics:

- Two or more relatives with the same type of cancer on the same side of the family – this likely aggravates the risk.
- Several generations affected – more the number of generations affected, more serious is the risk.
- Earlier age of cancer diagnosis than typically seen for that cancer type
- Individuals with multiple primary cancers
- The occurrence of cancers in one family, which are known to be genetically related, such as breast and ovarian cancer, or colon and uterine cancer and
- The occurrence of non-malignant conditions and cancer in the same person and/or family

Figure 5

CHARACTERISTICS OF SPORADIC VS. INHERITED CANCER IN SINGAPORE



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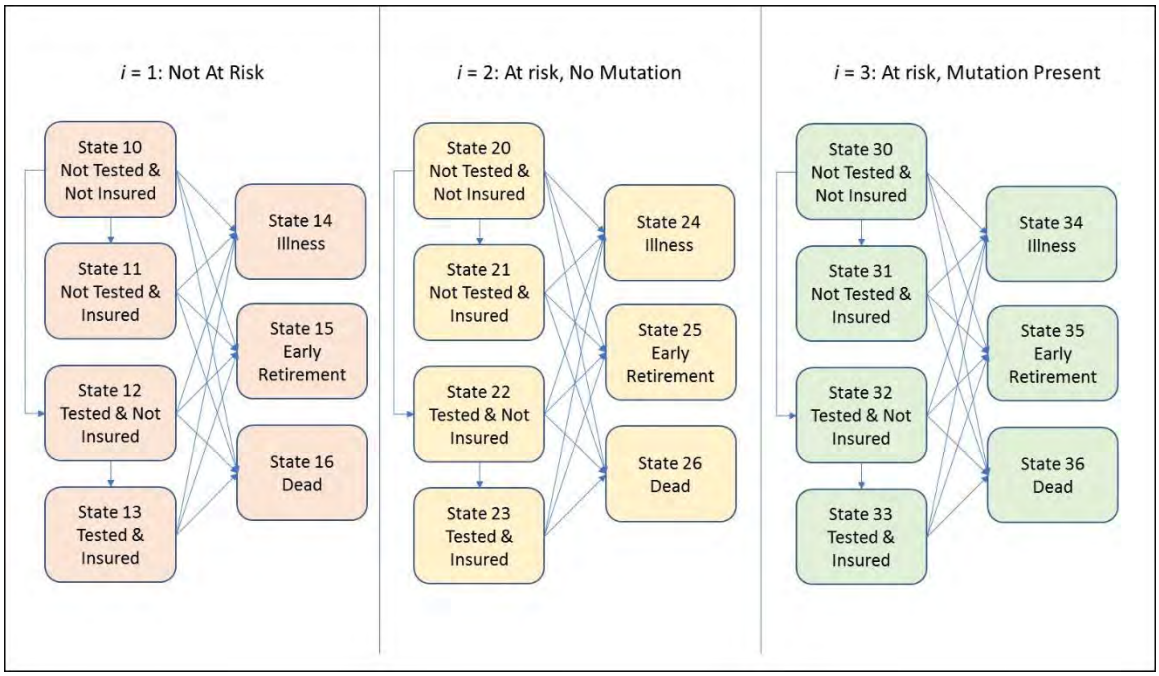
In general, given the difficulty in knowing and accessing family history, the probability that they carry a mutation must be estimated using Mendel's laws for descendants known to carry mutations. Genetic disorders are heterogeneous whether polygenic or monogenic. Some disorders may be caused by mutations in one of several genes, possibly with quite different penetration. With known family medical histories and advances in health care, many turn to genetic testing to ascertain risk of diseases, their progression and treatment options. Thus, the information is useful to develop strategies to manage health risk and aid in planning for the future.

Markov models provide promise on studying the impact of genetic testing. A sample age-wise model can be defined for population at time zero, for different family history.

Figure 6

MARKOV MODEL FOR TRANSITION WITH INSURANCE INCLUDING RETIREMENT PLAN



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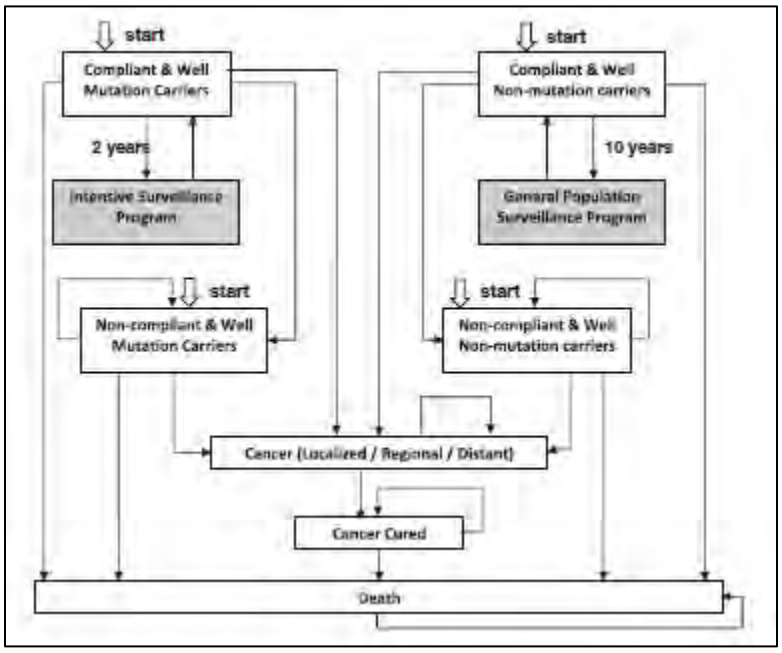
To estimate adverse selection, we can extend the models to retirement planning and insurance. A simple example is shown above with three sub-populations:

(a) persons with no family history and therefore not at risk of a genetic disease (i = 1)
(b) persons at risk because of family history but do not in fact have the mutation (i = 2) and
(c) persons at risk because of family history and have a mutation (i = 3).

The mutation frequency is represented by the proportions in each sub-population. For example, renal mutations occur in about 0.25 percent of population and at younger ages 0.25 percent would be at-risk carriers, 0.25 percent at-risk non-carriers and 99.5 percent not at risk. For older ages the mutation frequencies among healthy persons can be found by solving the Kolmogorov forward equations for the occupancy probabilities. However, to model life insurance we need survival rates after onset, which often depend on duration and age. Difficulty is in choosing the intensities relating to behavior. Research on attitudes to risk would help here. The basic tools for handling multiple-state models are differential equations: Kolmogorov's forward equations for occupancy probabilities, and Thiele's equations for prospective reserves. The usage of Markov models for predicting cancer among cohort of healthy 21 year old first degree relatives' mutation over life time in preventing hereditary nonpolyposis colorectal cancer (HNPCC) in Singapore suggests a lot of promise with combined cumulative risks of colorectal cancer at 32 percent (95 percent CI, 23–40 percent) by 50 years old, and 42 percent (95 percent CI, 30–52 percent) by 70 years old and lifetime risk for colorectal cancer of 43 percent compared to untested population[5].

Figure 7

MARKOV MODEL FOR TESTED VERSUS GENERAL POPULATION



Source: Duke NUS, Center for Health Services Research & Singapore General Hospital

To estimate the impact of DNA testing on a sample, we can first solve the differential equations, assuming no genetic testing and the control group are subject to baseline transition rates and experience mortality based on only family history. This gives the expected present value of benefits with "no use of genetic testing". We then solve the same equations, assuming genetic testing is allowed, and people experience the states at the same baseline transition rates. Net single premiums are paid in the same way, but transition rates are corresponding to people's genetic status if tested which would be baseline mortality if negative and extra mortality if positive, and only to family history if untested. This provides the expected present value of benefits in the full information case. The ratio of the two measures yields the cost multiplier of the impact of DNA testing, the ratio of what the true risk is to what is claimed and charged[6]. Then:

Cost Multiplier of DNA testing impact = EV (full information used) / EV (Allowable information used).

The force of transition at time t from state j to state k, for subgroup i, is denoted $\mu_t^{i,j,k}$. For each state, we wish to calculate, under a variety of assumptions, the actuarial present value of future insurance benefits, incorporating mortality and interest. This benefit reserve is a liability to the company. As the reserves for the various states are dependent, their values can only be found by solving a set of differential equations that generalizes Thiele's equation for benefit reserves. One differential equation can be written for each state for which there is an outward transition. The equation for state j can be written as:

$$d / dt\ V_t^{(1)j} = \delta_t V_t^{(1)j} - \sum_{k=j} (b_t^{jk} + V_t^{(1)k} - V_t^{(1)}) \mu_t^{jk}$$

where $V_t^{(1)j}$ = benefit reserve for state j at time t, δ_t = force of interest at time t, and b_t^{jk} = payment due upon transition from state j to state k.

Table 3

INCREASEDBENEFIT DUE TO A WOMAN WITH NO FAMILY HISTORY OF BREAST OR OVARIAN CANCER

		TERM			
Age	Increased Benefit	5	10	15	20
30	$2.00	1.0006	1.0021	1.0039	1.0054
30	$4.00	1.0009	1.0030	1.0056	1.0077
30	$10.00	1.0016	1.0057	1.0106	1.0145
40	$2.00	1.0008	1.0026	1.0042	1.0046
40	$4.00	1.0012	1.0037	1.0060	1.0066
40	$10.00	1.0023	1.0070	1.0112	1.0123
50	$2.00	1.0004	1.0013	1.0020	1.0021
50	$4.00	1.0006	1.0019	1.0029	1.0030
50	$10.00	1.0012	1.0035	1.0054	1.0056

Credit or permission line goes here.

For example, based on the family history and research, following is the medical protocol approved by the Singapore Ministry of Health for colorectal cancer and variants., which gives a good idea of the impact of family history on individual mortality/morbidity.

SI	Risk Group	Average Onset Age (years)	Frequency of Future Screening (in years)
1	Asymptomatic or family history limited to non-first-degree relatives	50	10
2	Colorectal cancer in first degree relative (parent, sibling) age 60 years or younger or two or more first degree relatives	10 years prior to youngest case in the family or age 40 years, whichever is earlier	5
3	Colorectal cancer in first degree relative over the age of 60 years	10 years prior to youngest case in the family or age 50 years, whichever is earlier	10
4	Personal history of colorectal polyps	3 years after polypectomy in the presence of high risk features (>1cm, multiple, villous architecture); otherwise, 5 years after polypectomy for low risk polyps	
5	Personal history of colorectal malignancy	One year after resection	3
6	Personal history of ovarian or endometrial cancer	One year after resection	Yearly
		High Risk	
7	Family history of familial adenomatous polyposis	10 to 12 years (from puberty)	Yearly
8	Family history of hereditary nonpolyposis colorectal cancer	20-25 years	Every 1-2 years

9	Inflammatory bowel disease a. Left-sided colitis b. Pan-colitis	a. From 15th year of diagnosis b. From 8th year of diagnosis	Every 1-2 years

Family history gives only an estimate to longevity and its use is limited at later ages. Lifestyle is more important to longevity. Most inherited conditions can be controlled through drugs, diet and exercise.

Section 3: Impact, Scope And Potential For Retirement Planning

DNA testing should be a useful tool for retirement planning also by answering the question *"Will I outlive my money?"* or *"How much longer can I work"* or *"What will be the status of my health post 70?"*. The answers are only the beginning of retirement planning.

With advances in genetics and computing, tools are available for a clearer picture of future needs. A Singaporean reaching 65 today can expect to live to 85 (male) and 88 (female) years[17]. After considering heredity, and lifestyle, DNA testing could be used to predict future health and elder care costs. With this knowledge, a financial plan can be adjusted between life-insurance saving and retirement planning more efficiently. Better still, one can plan to improve their longevity and add healthy years after retirement. One consensus is that the longer one delays claiming pension, the better return one gets. So, the knowledge about future health and longevity would be very helpful for retirement planning.

Insurance might be used to mitigate some financial risks. A better understanding of how genetic testing impacts mortality should help identify potential implications for insurance and provide useful information in shaping policy. Mostly only the applicant is aware of genetic results and family history and exposure of this information to an insurer is minimal. So, impact on preferred classification and change in policyholder behavior should be addressed. This aspect mainly affects:

1) Long Term Care insurance
2) Disability insurance
3) Critical illness insurance

Section 4: Any Regulatory Impact And Interventions

Insurance is based upon pooling of like risks and with asymmetric information, the need to address anti-selection is very important or insurers would find it difficult to cover claims with existing revenues. However, mandating genetic tests is problematic as insurance may be denied if the results are not positive. Anti-selection versus fear of insurance denial mostly applies to life insurance rather than health insurance because most developed countries offer government provided health insurance or mandate health insurance. If health insurance is provided to everyone, by definition, there can be no anti-selective risks.

While academic and medical communities continue to argue the merits of genetic exceptionalism, regulators are adapting to the influences of the media and society that genetic testing requires its own laws. Regulations typically fall into the following categories[3]:

1) No regulation
2) No regulation with written or unwritten codes of conduct from the insurance industry
3) Prohibitions on insurers requiring applicants to take a genetic test and prohibitions on discrimination if the applicant refuses to take a test

4) Prohibitions or moratoriums on using results from existing tests when policies are below certain limits
5) Prohibitions or moratoriums on using results from existing tests at all, sometimes including use of family history information

Countries having no regulation implies they consider genetic information to be pre-included with other medical information or have not yet found resources to enact regulation. Prohibitions could mean that governments do not trust the insurance industry to follow non-discriminatory practices post genetic testing. Those countries that have regulations prohibiting the use of results from existing genetic tests below certain limits seem to subscribe to the theory that some level of life, disability or long-term care insurance is an inalienable human right, vis-à-vis medical insurance, but above that limit is optional. Absolute prohibition or moratorium could mean regulators have a wait-and-see attitude. As new testing becomes more affordable and more widespread, life and health insurance companies need to monitor the emerging trends in genetic science closely. Working with regulators, medical professionals, industry groups and genetic advisors to agree on reasonable self-regulation in the field of genetics may be a prudent approach to staving off unwanted restrictive regulation.

Figure 8
PRESENT REGULATORY SCENARIO IN MAJOR ECONOMIES

Credit or permission line goes here.

It is encouraging to see the position taken by some of the regulators in this regard. For example, in Singapore the Bioethics Advisory Committee feels that there is little reason to suppose that the proportion of the population that can be accepted for insurance will suffer as a result of advances in genetic science as historic evidence shows that advances in medical knowledge have consistently contributed to improvements in mortality and a broadening of access to insurance. Certainly, insurers have no interest in narrowing the market for their products. On the contrary, they have every reason to welcome advances that improve the effectiveness of health management and make life insurance more affordable for all. The belief is that it is far more likely that a better understanding of the interaction between genetic makeup and environmental influences will have a positive impact on management and treatment which will result in further

improvements in mortality. With that premise, there is a clear coincidence of interest between life insurers and society as a whole in the successful development of genetic technology.

A mosaic of different regulations exists worldwide ranging from strict curbs in the use of genetic test results in most of Europe. At the same time, the Delhi High Court in India ruled that insurance policies could not exclude genetic disorders, raising hope that insurance companies will not be able to discriminate against people with genetic disorders and the judgment rules that the right to health insurance is a part of the fundamental right to life. But it has left the door open for insurance companies to exclude coverage for certain genetic disorders like Huntington's disease and Down's syndrome. Thus, in a judgment that contradicts itself, the court has implied that insurance companies cannot discriminate against their clients based on genetic heritage or disposition but can ask for higher premiums or deny claims if a genetic disorder has been established by appropriate medical testing. However, the Supreme Court of India[18] has stayed the order with the judgment that discrimination in health insurance against individuals based on their genetic disposition or genetic heritage, in the absence of appropriate genetic testing and laying down of intelligible differentia, is unconstitutional and violative of Articles 14 & 21 of the Indian Constitution.

In balance, it may be prudent to have structured regulation rather than leaving it unregulated so that the interests of both the customers, insurers and, above all, the society are protected.

Section 5: Opportunities For Society, Institutions And Individuals

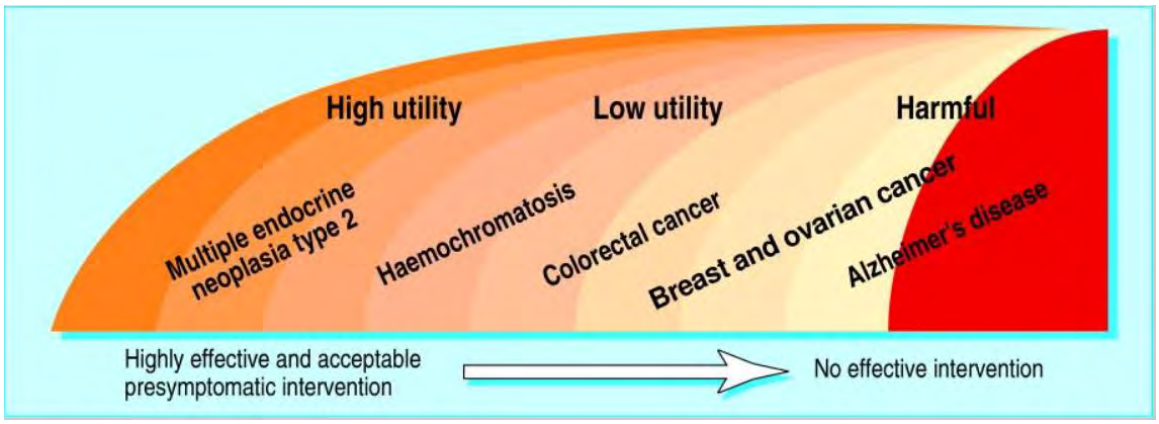
Genetic testing has come to stay, and it is imperative that it be used wisely as a predictive tool to improve the standard of life, price accurately and for better financial planning. It helps avoid unnecessary clinical investigations, help choose suitable therapy and allow future family planning. It also helps policy makers suitably tailor policy making and, for example, identify new beneficiaries or provide new value additions. For example, HSBC Insurance Hong Kong has added genetic health screening named ONEdna to its services as part of its protection solutions[15]. This is a saliva-based genetic screening service to allow customers to obtain better information about their health status and the various disease risks they may be susceptible to and allow for more accurate formulation of an optimal diet and deeper understanding of sensitivities to many common medications. The screening partner will not share or transfer customer data to HSBC Insurance Hong Kong without permission as data-security remains a priority. Prudential Singapore also offered myDNA scheme as a value-added service to customers with due protection to data. It is important to note that the myDNA result is not meant for underwriting or pricing purposes but is only a value-added feature provided for customers in Singapore. With a saliva sample, myDNA analyzes over 40 DNA markers related to how ones' body responds to the food one eats and the exercise one performs. This information allows customers to tailor their eating and exercise based on their DNA profile. It is further supplemented with an intuitive app which helps keep track of goals and provides a free phone consultation with a dietitian and an on-demand chat with a dietitian. Overall this helps the customers to better plan for better health and thus lead healthier lives.

Similarly, AIA Hong Kong had rolled out limited offers to support "Smart Elite Ultra" critical illness protection solution where policyholders of the "Smart Elite Ultra" plan together with an AIA Vitality Selected Insurance Product get a "fitlife Health Coaching Program and Genetic Test" to tailor their health program. A similar exercise is from Thailand's Muang Thai Life Assurance with the aim of helping their customers manage their lifestyles in return for more favorable pricing. Herein, at the start, consumers get a blood test, and are encouraged to do so in six-month intervals; if their glucose levels improve, their next premium is reduced. However, unlike in other cases, the data becomes the property of Muang Thai, which uses it for pricing.

Having said this, we need to realize that, with the present level of medical capabilities, the utility of genetic testing for intervention is not always positive. It is, in fact, a mixed bag with varying effectiveness in different diseases. These diseases range, as detailed in the figure below, from those for which testing is most useful through to those for which testing is least useful or even potentially harmful. So, it is possible that even the idea that there would be anti-selection is overestimated as medical intervention is not always possible or is even counterproductive. This overestimation of anti-selection may remain relevant until such time the predictive tests are further refined with respect to accuracy and the utility of medical intervention is also improved considerably[8].

Figure 9

UTILITY OF PREDICTIVE GENETIC TESTING FOR DIFFERENT DISEASES



Source: The complexities of predictive genetic testing[8]

A bigger point of interest would be the interaction and study of genetic, environmental and personal behavior. For example, how much of a person's overall health is explained by genetic factors and how much is caused due to environmental factors such as pollution levels, climate change and against all this how much is due to personal behavior such as lifestyle, occupation, stress levels etc. That would make for a much more comprehensive study with far reaching consequences and explain matters more holistically. Also, more than genetic predisposition other aspects like below mentioned could be more crucial:

(i) How susceptible to self-medication or how prone to antibiotic overdosing is the person?
(ii) How much of self-control and discipline does the person possess with respect to healthy living?
(iii) Intra-generational and inter-generational differences with respect to approach to life.

Section 6: Conclusion

Much of the impact of DNA testing is in handling the uncertainty it brings, and assumptions are needed in two categories: impact on consumer behavior, and impact on mortality and morbidity outcomes. Genomics, genetic testing, and precision medicine will play a rapidly increasing role in patient care and disease prognostication and ultimately lead to improvements in morbidity and mortality. Depending on the percent of the population undergoing genetic testing and variation in disease incidence based on polygenic risk scores, claim costs were projected to increase by approximately 1.8 percent and in-force lapse rates could average 0.5 percent. Latest research by the Canadian Institute of Actuaries indicates that a ban on using genetic information in critical illness (CI) underwriting would result in a 26 percent increase in the average CI claims rate[14]. While it is true that anti-selection as a consequence of predictive tests are a distinct reality, it

is still early to quantify this risk or the impact on population morbidity, mortality and lapse experience with certainty. The insurance industry needs to continue to support and promote the development of medico-actuarial research to gain a better understanding of the impact.

But is the absolute change of human behavior with respect to the results of a genetic test or medical advice a universal fact? The evidence available seems not to support this view; at least not wholly. In a 2016 review study published in the British Medical Journal, researchers analyzed over 10,000 abstracts and 18 studies to see if providing DNA-based information of disease risk to people would influence their behaviors to reduce said risks. Surprisingly, after the analysis, they discovered that people who were given DNA-based information on their disease risk, as well as how to lower their said risks, made little to no changes to their health behaviors in terms of improving their diet or physical activity, indicating that communicating such advice was inconsequential to changing people's health habits. So, it is safe to err on the side of caution and put in place reasonable legislations and regulations for this area for the health of the insurance industry as well as the society.

Access to genetic testing can improve patient care and could be incorporated into insurance products for policyholder benefit. DNA testing certainly provides an ability to predict all-cause mortality based on individual DNA and family history for the insurers and for the customers to do accurate financial planning but further study including AI is needed to further augment the results and appropriate regulations also are a critical need around this. One way out could be to increase reserves needed somewhat akin to the catastrophe reserves to handle this situation.

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