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Epigenetics: A White Paper on Technology and Innovation

Applying Modern Biotechnology to Life Insurance Underwriting

September 2020

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Applying Modern Biotechnology to Life Insurance Underwriting

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Section 1: Background and Scope

1.1 BACKGROUND

Epigenetics is a rapidly growing field in molecular biology that seeks to understand how gene expression – *i.e.,* whether a gene is turned "off" or "on" – is affected by changes unrelated to the changes in the underlying DNA sequence. As described by the researcher Conrad Waddington in 1942, the basic question for epigenetics ("epi" meaning "above") was to investigate how a given cell could differentiate itself as a certain *type* of cell, given that all cells contain the same DNA. The idea that a cell's fate might be controlled by other, external factors, besides the DNA sequence itself, has been and remains the fundamental premise of epigenetics.

Today, epigenetic science is part of a host of biotechnology tools helping transform healthcare into precision medicine. These same tools also offer exciting opportunities to modernize underwriting, with direct application in industries such as life and long-term care insurance. This paper explores how molecular biology, specifically epigenetics, may impact the life insurance industry, and considers the effects of utilizing epigenetic biomarkers for underwriting.

1.2 SCOPE

This White Paper provides an introductory overview of the topics listed below in the following order:

- What is the science of epigenetics and its trajectory as a technology?
- How is epigenetic information distinct from genetic information?
- How is epigenetic information obtained in practice?
- What criteria are used to evaluate epigenetic tests?
- What is the current state of epigenetic testing for life insurance underwriting?
- What areas of epigenetic research are applicable to underwriting?
- How might epigenetic testing be implemented in life insurance underwriting?
- What are some case studies that show the benefits of including epigenetic information in life insurance underwriting?
- How could epigenetics affect other parts of the life insurance business?
- What are the costs of accessing epigenetic information?
- What is the regulatory status of using epigenetics for insurance underwriting?
- What are the privacy and confidentiality considerations of using epigenetics for underwriting?
- What is the potential for racial bias (intentional or unintentional) in the usage of epigenetic information for underwriting?
- What is the status and ultimate potential of implementing epigenetic testing in the life insurance industry?

This White Paper does not intend to cover all aspects of the application of epigenetics to the life insurance industry. Specifically, this White Paper does not drive into deep technical or platform-dependent issues around particular epigenetic tests (e.g., PCR vs. micro-array vs. sequencing), but seeks rather to illustrate broadly and generally how epigenetic information could be compelling for the disciplines of insurance underwriting and risk classification.

Section 2: Epigenetics – Definition and Scientific Background

2.1 WHAT IS THE SCIENCE OF EPIGENETICS?

Epigenetics is a unique and growing scientific field within molecular biology that studies changes in gene expression and cellular function that are not due to changes in the underlying DNA sequence. As described by the developmental biologist Conrad Hal Waddington in 1942, epigenetics emerged as a framework to describe the idea of *cell fate*, or how it is that a given stem cell develops into a fully differentiated cell, when the underlying DNA sequence has not changed.

Waddington likened the process of cell development to a ball rolling down a hill; the hill contains many paths that the ball can roll down, with each path leading to a final differentiated state **(Figure 1)**.

Figure 1

THE EPIGENETIC LANDSCAPE OF WADDINGTON[1]

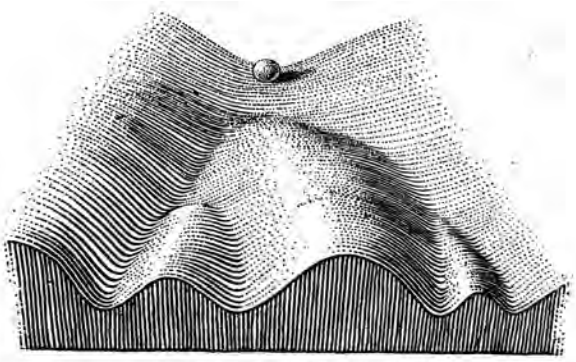


FIGURE 4

Part of an Epigenetic Landscape. The path followed by the ball, as it rolls down towards the spectator, corresponds to the developmental history of a particular part of the egg. There is first an alternative, towards the right or the left. Along the former path, a second alternative is offered; along the path to the left, the main channel continues leftwards, but there is an alternative path which, however, can only be reached over a threshold.

What comprises this "epigenetic landscape" is a host of molecules that regulate gene expression. To appreciate this concept, it's important to understand the basics of genetics. Genetic information provides the fundamental instructions for life and is contained in the molecule, DeoxyriboNucleic Acid (DNA). In turn, DNA is composed of a paired series of molecules known as nucleotide bases: adenine, cytosine, guanine, and thymine (A, C, G, and T). These base pairs comprise the double helix structure of DNA that composes our chromosomes. The order, or sequence, of these base pairs provides the blueprint for biological life.

Human DNA contains three billion base pairs, making up around 20,000 genes (though scientific consensus on the tally continues to fluctuate). Genes are specific sequences of base pairs that provide instructions on how to make proteins—complex molecules that trigger various biological activities and structures. Genes, therefore, provide the instructions for the baseline characteristics of any cell, organism, or individual. For example, variations in human genes lead to different characteristics such as hair color, height, skin color, etc. However, whether, when, how, and where

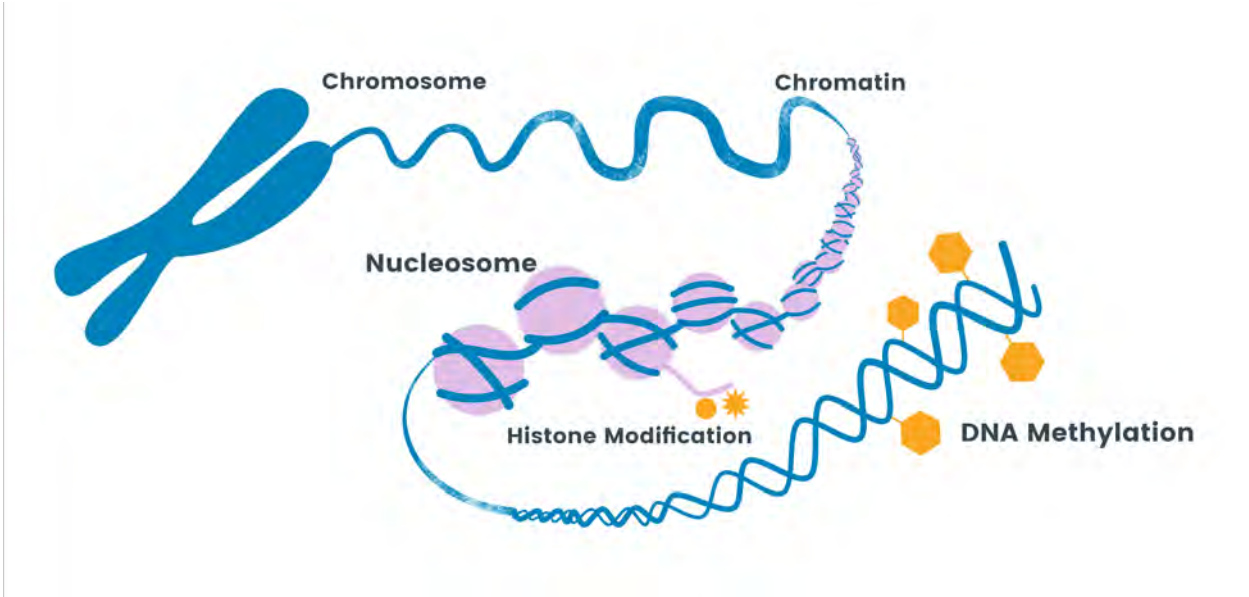
[1] Waddington, C.H. The Strategy of the Genes (Geo Allen & Unwin, London, 1958)

a particular gene is expressed or suppressed is a function of other mechanisms. Epigenetics is the study of these mechanisms.

The prefix "epi" is derived from Greek and means "over, above, or upon." Accordingly, epigenetics refers to a region beyond the DNA sequence (*i.e.,* the epigenome). Whereas the genome is composed of a sequence of DNA molecules, the epigenome can be understood as a separate universe of chemical modifications that may attach onto individual nucleotide bases, or proteins, that bind to DNA known as histones. The two main types of epigenetic "marks" are methylation and histone modification.[2] The addition of these modifications can cause a certain portion of genetic instructions to be "switched on/off."

Figure 2

VISUALIZING HUMAN DNA AND EPIGENETIC MODIFICATIONS[3]



Today, it is understood that mechanisms like DNA methylation are central to both normal cellular development and function, as well as dysfunction and disease development; and further, that they can leave distinct patterns along the epigenome that can be tied back to factors such as age, health status, and even behaviors (e.g., smoking, exercise, diet, and drug use).[4]

2.2 WHAT IS THE HISTORY AND TRAJECTORY OF EPIGENETIC SCIENCE AND TECHNOLOGY?

The trajectory behind epigenetic science and technology is closely tied to the recent advancement of biotechnology. Up until the early 2000's, relatively little had been done to study epigenetics. Epigenetic research on a widespread basis was enabled by the commercialization of micro-array and "next-generation" sequencing technologies and bioinformatic methodologies, which have matured in terms of cost effectiveness and adoption.[5]

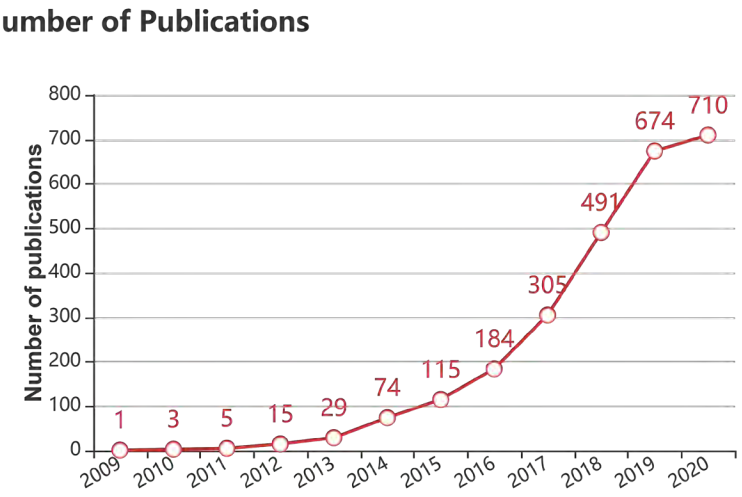
[2] (Handy, Castro, and Loscalzo 2011)
[3] (Linnér and Almgren, 2019)
[4] (Jin, Li, and Robertson 2011); (Wei et al. 2017)
[5] (Shendure et al. 2017);

The early methods for sequencing DNA were established during the 1970s. The most notable of these developments was Frederick Sanger's 'chain-termination' method, or simply Sanger sequencing. In the 1980s, newer technologies emerged that allowed for the simultaneous sequencing of hundreds of samples at a time. These first-generation sequencing technologies helped to produce the first human genome in 2003, funded by the U.S. government at a cost of $3 billion dollars.[6]

Today, the human genome can be sequenced at a cost of less than $1,000, with "next-generation" or "second-generation" sequencing allowing the study of molecular health in ways that were inconceivable a decade earlier. Emerging in the 1990s and becoming commercially available in the 2000s, these "massive parallel sequencing" approaches, as well as tools such as micro-arrays, have opened up a vast area of genetic and epigenetic research due to their ability to scan millions and billions of base pairs at a time. These tools have enabled vast research into patterns of DNA sequences and DNA methylation that differ between normal and diseased states and have yielded an abundance of peer-reviewed, scientific studies called genome-wide association studies (GWAS) and epigenome-wide association studies (EWAS), as shown in **Figure 3**.

Figure 3

NUMBER OF PUBLISHED EPIGENOME-WIDE ASSOCIATION STUDIES[7]



Both GWAS and EWAS examine the associations between molecular variants with certain traits such as disease, cell function, and health status. EWAS research papers have specifically provided substantial evidence that external environmental and lifestyle factors leave identifiable patterns of methylation across the epigenome.

In today's world of "Big Data," the importance of artificial intelligence and machine learning on molecular research cannot be overstated. The availability of large-scale computing, new algorithms and bioinformatic techniques allow for troves of biological data produced by next-generation sequencing and micro-arrays to be analyzed to find existing molecular markers ("biomarkers") associated with health and disease, as well as predict future disease risk. New innovations are being rapidly developed to understand whether and how DNA methylation and other epigenetic changes offer insights into the diagnosis and treatment of diseases, including cancer, Alzheimer's, and aging itself.

[6] (Hood and Rowen 2013); (Gannett 2008); (Heather and Chain 2016)
[7] (Linnér and Almgren, 2019)

The full potential understanding of molecular biology and epigenetic mechanisms in health and disease has yet to be fully realized.

2.3 HOW IS EPIGENETIC INFORMATION DISTINCT FROM GENETIC INFORMATION?

Genetics and epigenetics look at different parts of our biology. Genetic information is focused on the sequence of the A, C, T, and G molecules that make up the base pairs in an individual's DNA, including the presence or absence of specific mutations (changes to the base sequence that can cause variations in the instructions resulting in certain diseases). By contrast, epigenetic information involves the presence or absence of chemical modifications that may affect the processes of gene expression and translation into proteins without altering the DNA sequence itself.

The genes an individual receives at birth from his or her parents are the permanent, immutable instructions of their biology, factors over which an individual has no control. By contrast, an individual's epigenome may change over time based on factors such as aging, exposure to environmental pollutants, and using tobacco, alcohol, or other drugs. Many epigenetic modifications have the property of reversibility (for example, a methylated site along the epigenome can become unmethylated and back again). An epigenetic test that seeks to take a snapshot of an individual's health with regard to behavioral or lifestyle factors would be qualitatively different from genetic testing that examines factors over which an individual has no control.[8]

In this sense, epigenetic testing could be considered to simply bring better technology to bear on assessing traditional health factors and behaviors currently obtained from clinical laboratory testing. This application would be consistent with well-established norms in life insurance underwriting. On the other hand, others have argued that genetics and epigenetics are entangled with one another, which is relevant in discussions around biological mechanisms, such as for therapeutic drug targets. But for the purposes of estimation and classification, pattern recognition of epigenetic signals rather than its interactions with genetic variants has been the focus of relevant commercial applications of the technology.

2.4 HOW IS EPIGENETIC INFORMATION OBTAINED IN PRACTICE?

Several options exist for the quantification of epigenetic data. These options are selected based on a confluence of factors, including price, level of accuracy, reproducibility, biospecimen requirements, and the breadth and depth of measurement. Specifically, for DNA methylation, commonly used platforms include bisulfite sequencing, micro-arrays, and methylation-specific polymerase chain reaction (PCR)-based solutions.

Micro-array technology has been the workhorse for large-scale, population research and commercial products with genomics and epigenetics. A micro-array is a glass slide with nucleotide probes that can detect the DNA sequence (for genetic analysis) or methylation status (for epigenetic analysis). Micro-array technology is the basis of the direct-to-consumer molecular health and wellness testing industry. Companies such as 23andMe (genetic health), Viome (microbiome health), and Muhdo (epigenetic health) all use micro-array technology to support their businesses.[9] At relatively low costs, these tests can reveal factors of an individual's health and wellness, some of which have high

[8] *See, e.g.*, https://www.nature.com/articles/ncomms14617 ("[I]t appears worthwhile pointing out that prevention of or intervention on smoking-related DNAm changes may provide major improvement in premature death prevention, given the reversibility of smoking-induced methylomic aberrations.").
[9] Regalado, A. (2020, April 2). More than 26 million people have taken an at-home ancestry test. https://www.technologyreview.com/2019/02/11/103446/more-than-26-million-people-have-taken-an-at-home-ancestry-test/

prevalence and influence mortality factors.[10] Companies such as Thermo Fisher Scientific and Illumina are major suppliers of micro-array technology.

Micro-arrays are an efficient method of quantification that selects important, specified locations on the genome or epigenome instead of sequencing all three billion base pairs of DNA. The location of each probe on the array records a single variant at a specific site. In genetic arrays, these variants are called single nucleotide polymorphisms (SNP). In epigenetic arrays, these are called CpG sites, representing cytosine (C) and guanine (G) bases joined by a phosphate group. When a DNA specimen (derived from blood or saliva, for example) is washed over the micro-array, sites that match the probes are picked up by the array and are detected by a laser scanner. This technology allows information from a large number of SNPs or CpGs to be efficiently queried at scale, but have the downside of returning much less information compared to sequencing.[11]

Sequencing-based approaches are considered the gold standard when it comes to accurate measurement of DNA methylation levels and detecting less abundant (epi)genetic events, such as circulating tumor DNA in a liquid biopsy. Commonly used sequencing approaches for DNA methylation include whole genome bisulfite sequencing, reduced representation bisulfite sequencing, and pyrosequencing. Sequencing approaches that target specific regions of the epigenome are now available, which can reduce sequencing costs. Downsides to sequencing include its scalability, which is partly due to the fact that it is labor intensive both in the laboratory and computationally.

Since its advent in 1984, PCR has been a mainstay technique used in molecular biology. It is based on identifying and amplifying specific regions of the genome that one can target with custom probes. PCR-based methods are particularly advantageous because they are cost-effective and commercially scalable. However, currently, PCR assays are unable to measure more than a handful of sites along the genome or epigenome.

2.5 WHAT CRITERIA ARE USED TO EVALUATE EPIGENETIC TESTS?

There is a widely recognized framework for evaluating clinical tests which can be applied to evaluating epigenetic tests. This evaluation framework is comprised of three key headings: *analytical validity*, *clinical validity*, and *clinical utility*:

- Analytical validity refers to how well the test predicts the presence or absence of a particular epigenetic change. In other words, can the test accurately detect whether a specific epigenetic variant is present or absent?

- Clinical validity refers to how well the epigenetic variant(s) being analyzed is related to the presence, absence, or risk of a specific disease.

- Clinical utility refers to whether the test can provide information about diagnosis, treatment, management, or prevention of a disease that will be helpful to a consumer.[12]

The *analytical validity* of a test is often assessed with gold standard measures. Gold standards, however, must be appropriate to the purpose of an epigenetic test. For instance, when a direct measure is needed to determine methylation levels at specific epigenetic sites, bisulfite sequencing is generally considered the gold standard. However,

[10] SOA, The Impact of Genetic Testing on Life Insurance Mortality. October 2018.
[11] (Norrgard 2008)
[12] Adapted from the NIH's Genetics Home Reference, "How can consumers be sure a genetic test is valid and useful?" July 28, 2020. https://ghr.nlm.nih.gov/primer/testing/validtest

if a test's output is to distinguish between groups of subjects with and without a disease, the standard of comparison must refer to other clinical measures used to diagnose disease and/or assess disease progression. In this case, selecting an appropriate clinical gold standard is important because it will affect the observed performance of the test.

For a laboratory to establish *clinical validity* for a DNA methylation test, it must establish performance characteristics that include an analysis of accuracy, precision, analytical sensitivity, analytical specificity, reportable range, reference interval, and any other performance characteristics required for the test system in the laboratory that intends to use it.[13] Few epigenetic tests are presently used in clinical settings. Most, if not all, commercially available epigenetic tests are focused on cancer diagnosis, screening and early detection. Over a dozen DNA methylation biomarkers are currently registered in the marketplace, most of them simple in construction, measuring only one or a few loci.[14] The overwhelming utility of these indicators is the potential for the methylation analysis to be carried out on an easily accessible biospecimen (*e.g.,* blood or stool), rather than being limited to invasive tissue biopsies.

While analytical validity involves comparing the test output to a reference standard, clinical validity involves comparison of the processed test result with the clinical disease or trait that it seeks to detect. Clinical validation measures, such as sensitivity and specificity, should be based on an independently gathered set of samples that ideally match the target population and the manner in which the test will be conducted in practice. Failure to do so may result in biased measures of performance.

[13] Implementation of DNA methylation analysis in clinical laboratories – whether by sequencing or other assays – is often accomplished through Laboratory Developed Tests (LDTs) that are developed by and deployed within a single clinical laboratory. The Centers for Medicare & Medicaid Services (CMS) regulates all non-research laboratory testing on humans in the United States through the Clinical Laboratory Improvement Amendments (CLIA), and ensures that LDTs meet required performance specifications and quality assurance standards.
[14] (Locke et al 2019)

Section 3: Impact of Epigenetics on Insurance

3.1 WHAT IS THE CURRENT STATE OF EPIGENETIC TESTING IN LIFE INSURANCE?

Epigenetic testing has only started to be explored for life insurance underwriting, but its advocates believe it to be a tool that holds promise to pave the way for more precise underwriting and more personalized life insurance premiums. According to a report from industry research firm, Capgemini, the key drivers for the adoption of epigenetics include speeding up insurance delivery, enhancing the customer journey with non-invasive testing, and developing innovative life insurance products.[15]

3.2 WHAT AREAS OF EPIGENETIC RESEARCH ARE APPLICABLE TO LIFE INSURANCE UNDERWRITING?

The top ten areas studied in epigenetic studies reported to the National Genomic Data Centers are:

1. Smoking
2. Aging
3. BMI
4. Type 2 Diabetes
5. Maternal smoking
6. Alcohol consumption
7. Waist circumference
8. Breast cancer
9. Gestational diabetes
10. Depression

For each of these areas of health, disease, and behaviors, as well as others, epigenetic biomarkers could be developed to test an individual applicant for the presence or absence of a given trait. Since a substantial body of epigenetics research seeks to understand the behaviors and risk factors associated with "lifestyle diseases" and its resulting impact on aging, much epigenetic research has direct application to the medical underwriting of risk factors. Thus far, the early commercialization of epigenetic tests for life underwriting has focused on the areas of smoking and alcohol consumption.

3.3 HOW MIGHT EPIGENETIC INFORMATION IMPACT UNDERWRITING PRACTICES?

Important early investigations into the dynamics of human mortality can be traced to Edmond Halley's *Estimate of the Degrees of the Mortality of Mankind* (1693) and Benjamin Gompertz's *Nature of the Function Expressive of the Law of Human Mortality* (1825). Since then, actuaries and underwriters have worked to better understand human longevity and mortality to provide better predictive models and actuarial estimates.

The effort to develop better mortality underwriting models has resulted in the development of medical underwriting protocols involving the collection of biological fluids (*i.e.,* blood and urine) and detailed medical records designed to better understand the health of an applicant under consideration for life insurance. More recently, the desire to create a faster and easier underwriting process has spurred movement within the industry toward fluidless or accelerated underwriting programs.

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[15] Capgemini. Top Trends in Life Insurance: 2020. https://www.capgemini.com/wp-content/uploads/2019/11/Life-Insurance-Trends-Book_2020.pdf

Broadly, accelerated underwriting programs seek to use multiple sources of third-party data as the basis of underwriting the individual health of an insurance applicant. These sources of information span a range of existing, emerging, and still-to-come data—such as motor vehicle and criminal history records, credit scores, electronic health records, or even analytics derived from wearable technology or insights from social media.

But accelerated underwriting programs aren't perfect. Due to the recency of the adoption and application of many of these data sources, there is little credible mortality data to indicate how these accelerated practices are performing in terms of underwriting efficacy. Moreover, there is concern about how these data sources that can be used to assess mortality will, in fact, perform as predictors of mortality in the long-term. As such, insurance carriers are conducting post-issue testing or using other means in order to find early indications of accelerated underwriting program performance. Regulators have also expressed concerns over the practice of using "data, algorithms, and models that purport to predict current health status on a single or limited number of unconventional criteria" due to worries about transparency, and unfair discriminatory or actuarially unsound results.[16]

Recent challenges brought about by the COVID-19 pandemic have only hastened the trend toward accelerated underwriting. The pandemic has strongly interfered with or halted the traditional paramedical collection of fluids, which represents the insurers' primary method of obtaining specific health information on an applicant. The disappearance of this medical information and difficulty acquiring attending physician statements for underwriting has increased reliance on accelerated underwriting practices.

Epigenetic information may help to bridge the gap between traditional and accelerated underwriting practices with non-invasive saliva testing that further supports or enhances accelerated underwriting programs by providing both a convenient underwriting process, as well as specific biological health data for accurate underwriting and risk classification. Researchers expect that it's possible that a simple saliva test could produce the type of accurate specific health information obtained through traditional medical screening, as well as provide new risk factors not otherwise obtainable from traditional laboratory tests, or otherwise emerging from new health technologies.

3.4 HOW MIGHT EPIGENETIC TESTING BE IMPLEMENTED IN LIFE INSURANCE UNDERWRITING?

Like traditional medical underwriting, epigenetic tests require access to a biological specimen. Although specimen collection sacrifices speed, it provides additional information for underwriting and risk assessment. One benefit that epigenetic testing may provide over traditional methods is the opportunity to use saliva rather than blood to glean applicant health information.

Saliva specimens may provide sufficient epigenetic information to meaningfully enhance accelerated underwriting. A saliva specimen could be collected in a variety of ways, such as by an agent, notary, paramedical technician, retail pharmacy, or self-collected by the consumer, as is currently done for direct-to-consumer genetic tests. Saliva has the advantage of being easily shipped through mail, which may be useful in situations where paramedical services are unavailable. This approach could improve turnaround times in a noninvasive manner, while providing information that could supplement or even substitute for traditional lab screens.

If a specimen is self-collected and shipped, safeguards against fraud could be put in place. It is plausible that epigenetic information regarding age and sex could be derived from the specimen itself to match against the applicant's self-reported information as a way to verify 'molecular chain of custody.' Insurers could also explore logistical solutions

[16] Insurance Circular Letter No. 1 (2019): Use of External Consumer Data and Information Sources in Underwriting for Life Insurance. (n.d.). Retrieved from https://www.dfs.ny.gov/industry_guidance/circular_letters/cl2019_01

such as using electronic signature and video confirmation procedures. Even more, insurers could find creative ways to align incentives with consumers, for example by returning epigenetic information back to consumers as one form of a value-added and personalized health and wellness offering (see section 4.1).

If blood is used to derive epigenetic information, then the specimens could simply be collected through existing paramedical procedures currently used in fully underwritten cases. Again, the epigenetic information could be used to enhance, supplement, or substitute for existing tests, as well as provide new health insights unobtainable from any other technology to date.

Whether through blood or saliva, epigenetic information could either be implemented into a traditional underwriting protocol as a replacement for paramedical examinations, or integrated into an accelerated underwriting program as a backup data layer providing similar inputs found in traditional laboratory screens, as well as supplementary data with novel insights into health.

3.5 WHAT ARE SOME CASE STUDIES THAT SHOW THE BENEFITS OF IMPLEMENTING EPIGENETIC INFORMATION IN LIFE INSURANCE UNDERWRITING?

Epigenetic information can provide a host of information currently provided by traditional measures of health obtained from clinical chemistry panels, as well as new biomarkers that enhance mortality risk assessment. Epigenetics could provide indicators for traditional measures, or for new biomarkers not captured by existing current blood or urine tests. With regard to new markers, two well-published areas of epigenetics related to mortality risk are: (i) former tobacco use; and (ii) biological aging.

The following two case studies examine how epigenetic biomarkers may provide new insights on traditional measures of health, as well as provide new health markers to enhance mortality risk assessment.

1. Traditional Measure of Health: Tobacco Use

Since the 1960s, tobacco use and exposure has been documented by scientists as harmful to human health.[17] Despite this knowledge, actuarial tables that distinguished between tobacco users were not developed until the 1980s.[18] Today, 19% of the American population uses tobacco, and smoking remains a leading cause of preventable illnesses that cause an estimated 480,000 deaths per year in the United States.[19] Although the prevalence of smoking is lower among insured populations, tobacco use remains one of the most important risk factors for developing serious conditions such as heart disease, lung disease, and cancer. Due to its influence on health, underwriting places significant value on identifying tobacco exposure among life insurance applicants.

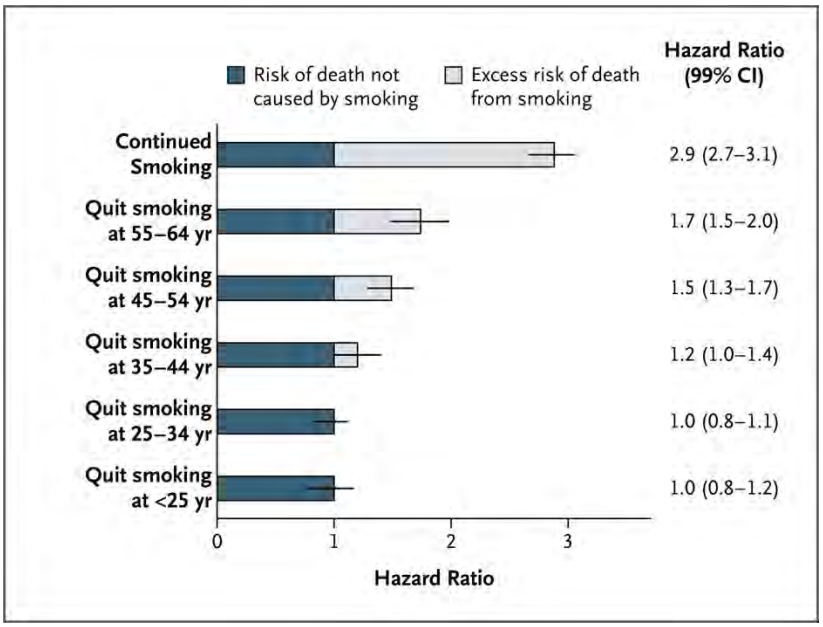
Accordingly, the life insurance industry widely screens for tobacco use by testing with the biomarker *cotinine*, a metabolite of nicotine, in an applicant's clinical chemistry panel. The challenge with measuring cotinine biomarkers is its short half-life of approximately 16 to 19 hours.[20] A life insurance applicant who can forgo tobacco use for a few days can pass a cotinine test as a "non-smoker" and significantly save on future annual premium payments. Within the industry this is known as "smoking amnesia," which ultimately results in non-smokers picking up the cost.

[17] (Weir and Dunn 1970)
[18] (Miller and Gerstein 1983); (Benjamin and Michaelson 1988)
[19] Fast Facts. (2020, May 21). Retrieved from https://www.cdc.gov/tobacco/data_statistics/fact_sheets/fast_facts/index.htm
[20] (Jarvis et al. 1988)

Another challenge with the cotinine test is that it does not reflect the amount of tobacco smoked. In other words, beyond a self-report from an applicant, underwriters have no means to distinguish between whether an applicant is for instance a never-smoker versus a recent quitter who smoked two packs a day for the past twenty years; or distinguish between someone who smokes a pack a week versus someone who smokes a pack a day. The life insurance industry dichotomizes tobacco use between current and recent users versus past and never users. However, numerous studies have demonstrated a continuum of health and mortality impacts depending on how long and how much someone has been a smoker **(Figure 4)**. Misclassifying long-time former smokers who quit merely a year or two prior to applying to life insurance could lead to substantial excesses in mortality risk that would not transpire until decades after the policy has already been issued. This presents problems in correctly assessing mortality risk and establishing premium rates for non-smokers, smokers, and former smokers.

Figure 4

RISKS OF DEATH FOR PARTICIPANTS WHO CONTINUED TO SMOKE AND FOR THOSE WHO QUIT SMOKING ACCORDING TO AGE AT THE TIME OF CESSATION [21]



Contrast this with the use of epigenetic biomarkers for detecting tobacco usage. Methylation markers associated with tobacco use persist years after smoking cessation and can, therefore, serve as a stable biomarker of lifetime exposure to tobacco.[22] Furthermore, these epigenetic markers of smoking have been shown to be usage dependent and likely reversible, with smoking-induced demethylation reverting as a function of abstinence.[23] The ability to quantitatively measure tobacco exposure through methylation markers opens the door to developing epigenetic tests that can discriminate more precisely between current, former, never, and heavy smokers.

Epigenetic biomarkers that provide further insights into an insurance applicant's tobacco usage stand to provide improved insights for underwriting that traditional measures cannot. Thus, epigenetic biomarkers differ materially from cotinine biomarkers in that they are able to provide greater utility by more direct measurement of the core

[21] (Linnér and Almgren, 2019)
[22] (Joehanes et al. 2016); (Zeilinger et al 2013)
[23] (Philibert et al. 2020)

aspects of traditional measures of health (*e.g.,* long-term tobacco use) by capturing new dimensions of tobacco use, which can enable more accurate segmentation of applicants based on mortality risk.[24]

2. Novel Biomarker of Health: Biological Age

Biological age is a measure of lifestyle, habits, and innate factors that cause us to age. How an individual's biological age should be measured and what factors should be included and weighted to calculate a biological age continues to be of great interest to researchers.[25] Today, it is understood that individuals experience different rates of aging resulting from progressive deterioration, occurring simultaneously at the molecular, cellular, tissue, organ, and functional levels.[26] This is manifest in our daily lives as people of the same age develop age-related diseases and, ultimately, die at different ages.

While many approaches to quantifying biological age have been proposed, no approach has received more attention than the "*epigenetic clock*."[27] Beginning in 2011, researchers published a series of papers detailing the discovery of an epigenetic clock that uniquely tracked chronological aging. These articles highlighted the fact that "from the moment of conception, we begin to age," causing our cellular structures, gene regulation, and DNA sequence to decay.[28] The discovery of the epigenetic clock showed that epigenetics could be used to measure the cumulative effect of aging on our biological system, and with significant implications for developmental biology, cancer, and aging research.[29]

Since the discovery of the epigenetic clock, researchers have developed a number of different 'clocks,' each with their own unique attributes, but most shown to be associated with risk of mortality and age-related diseases, even after accounting for chronological age.[30] These clocks accounted for chronological age by taking the differential between epigenetic age and chronological age—with the difference referred to as epigenetic age 'acceleration' or 'deceleration.' The mortality associations have held true across racial/ethnic groups, body mass categories, sexes, smoking classes, physical activity status, cancer status, coronary artery disease status, or diabetes status.[31] Scientists still do not fully understand the underlying mechanisms between biological changes and epigenetic age acceleration, but the linkage between epigenetic biomarkers of aging and mortality has been firmly established in numerous populations around the world.[32]

To illustrate the implications of the epigenetic clock on underwriting and risk classification, we have constructed the following applied example below **(Figure 5)**. This example seeks to demonstrate how the epigenetic age acceleration could be applied in a life insurance underwriting scenario. For purposes of simplicity with this example, we have assumed that the age acceleration effect estimate (*i.e.,* hazard ratio) would be applied as a multiplier to the mortality estimate of the individual that resulted from traditional underwriting.

[24] (Moore 2020)
[25] (Jackson, Weale and Weale 2003)
[26] (Hayflick 2002)
[27] (Gibbs 2014)
[28] (Hannum et al. 2013); (Bocklandt et al. 2013)
[29] (Horvath 2013)
[30] (Lu et al. 2019); (Levine et al. 2018)
[31] (Chen et al. 2016)
[32] (Fransquet et al. 2019)

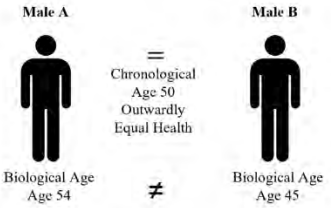
Figure 5

ADJUSTING MORTALITY RISK BY APPLYING EPIGENETIC AGE ACCELERATION MEASURES. (SEE EXHIBIT A FOR THE SUPPORTING MATHEMATICAL BASIS)

Applied Example.

Assume two fifty-year-old males (Male A and Male B) are by all outward appearances equal in terms of their health and wellness such that they are both underwritten and rated a standard mortality risk.

Assume further, however, that their epigenetic clocks measured with EEAA indicate that their biological age acceleration or deceleration rates are found to be two standard deviations from the mean of chronological aging. This would be tantamount to Male A and Male B, who are both chronologically aged 50, having biological ages of persons aged 54 and 45, respectively.



Assuming the EEAA all-cause mortality hazard ratio is a final adjustment to their mortality risk, the net effect of overlying EEAA to the mortality risk of Male A and Male B is:

- Male A, is now seen to be actually closer to a Table B mortality risk; and
- Male B, is now seen to be actually closer to an Extra Preferred mortality risk.

How does this result translate to the pricing mortality risk? Assuming both Males purchased life insurance policies with a death benefit of $1,000,000 with an interest rate applicable to the pricing of 1%, the insurance company that better classifies Male A as Table B mortality risk could expect to avoid ~$32,000 in claims over the next ten years; while Male B with his Extra Preferred mortality risk could expect to save ~$27,000 in lower premiums over the next ten years.

Underwriting Class	% of Standard	Mortality Risk	Adjusted Mortality Risk
Preferred Ult	0.25	0.00126475	
Extra Preferred	0.50	0.00252950	Male B 0.00312877
Preferred	0.75	0.00379425	↑
Standard	**1.00**	**0.00505900**	↓
Table A	1.25	0.00632375	0.00698549 Male A
Table B	1.50	0.00758850	
Table C	1.75	0.00885325	
Table D	2.00	0.01011800	
Table E	2.25	0.01138280	
Table F	2.50	0.01264750	
Table G	2.75	0.01391230	

Research into epigenetic clocks has found populations have normalized distribution of accelerating and decelerating clocks, meaning over 1/3 of the population is two standard deviations from mean chronological aging as illustrated in this example.

These case studies seek to illustrate how epigenetic biomarkers could be used to enhance traditional measures of health, as well as provide new health markers to enhance mortality risk assessment. Though presented as separate cases, epigenetic age acceleration measures can be used in conjunction with other epigenetic tests for tobacco use, alcohol, or other disease/health states because they capture different aspects of health and, as such, have been shown to have independent contributions in their mortality associations.[33] Moreover, epigenetic biomarkers could be used in conjunction or combination with traditional data sources. More work remains before epigenetic biomarkers converge with mortality underwriting, but the results and insights gathered thus far offer promise and point to an era of modern underwriting and risk classification.

[33] Though presented as separate cases, epigenetic tests for substance use and biological aging could be used in conjunction with one another, due to the fact that models combining biomarkers of epigenetic aging, as well as biomarkers of substance use, appear to predict mortality better than either predictor by itself. See *e.g.* (Mills et al. 2019)

Section 4: Future Status of Epigenetics in Insurance

4.1 HOW COULD EPIGENETICS AFFECT OTHER PARTS OF THE LIFE INSURANCE BUSINESS?

Relative to other financial and consumer products, life insurance is a product with low consumer involvement and a decreasing level of concern.[34] The insurance industry has struggled to build consumer loyalty or engagement. In one survey of consumer sentiment, life insurance had a greater negative emotion associated with it than home, health, auto insurance, and financial investments.[35] Life insurers are aware of the need to deliver richer value propositions to strengthen consumer experiences, which has led to greater attention and investment in programs to enhance customer engagement and satisfaction.

In addition to potentially creating a low-friction underwriting process for consumers and agents, and adding protective value to underwriting, epigenetic information may create new models of engagement with insurance customers. A wellness program using epigenetics could offer participants the opportunity to assess the molecular impacts of their habits and measure the progress from their efforts over time. As opposed to other biomarkers of health, epigenetic testing has the added advantage of being ascertained simply through a mail-in saliva sample. A program that provides a baseline measure, suggests practices for improvement, and measures the performance after program completion could provide substantial value to the consumer beyond-death protection. Insurers would need to assess the costs, benefits, and capabilities of such a program, but it is one way to potentially engage with consumers around their health and align the interests of both consumers and insurers towards living longer, healthier lives.

4.2 WHAT ARE THE COSTS OF ACCESSING EPIGENETIC INFORMATION?

A key consideration toward whether epigenetic tools will be commercialized in underwriting is the cost of the test. Excitingly, the costs involved in genetic screening technologies have dropped faster than what might have been predicted by Moore's Law.[36] Today, direct-to-consumer genetic testing companies offer health screening panels that cost anywhere from $199 to $299, and the costs for epigenetic tests are comparable.

In order to justify the cost of underwriting, early applications of epigenetic screening tests may be limited to situations such as larger face-value insurance policies, or in situations where the test can be used independently from other costly health screening tools. Depending on the expected value derived from the test in a given underwriting instance, epigenetic tests could be administered either in parallel or in place of a full paramedical exam. The latter would be more cost effective than the former, since the cost of paramedical tests would be replaced by the cost of the epigenetic test. As prices for epigenetic testing continue to fall, advocates of epigenetic technology are confident that it is only a matter of time before underwriting applications emerge as economically feasible in one manner or another.

4.3 WHAT IS THE REGULATORY STATUS OF USING EPIGENETICS FOR INSURANCE UNDERWRITING?

Policymakers have shown concerns that genetic information could be used prospectively to penalize individuals with increased risk of developing future diseases, even though they are otherwise healthy and there is no evidence of

[34] 2018 Insurance Barometer Study, LIMRA & Life Happens.
[35] Ferrante-Schepis, Maria. "Flirting with the Uninterested," Advantage Media Group (2012), pp. 16-17
[36] (Muir et al. 2016)

disease.[37] These concerns have led to the federal Genetic Information Nondiscrimination Act (GINA), which generally prohibits the use of genetic information by health insurers. Life insurance is explicitly exempted from GINA. State law, on the other hand, in at least 30 states, does have laws regulating the use of genetic information in life insurance. These laws are largely procedural in nature, such as requiring informed consent, but some do purport to place limits on the substantive use of genetic information, with at least two states preventing insurers from mandating that applicants take a genetic test to obtain life insurance, but allowing it voluntarily, and one state, Florida, passing substantial restrictions to using genetic testing in any manner for insurance purposes.[38]

Do laws regulating genetics also apply to epigenetics? While clear regulatory guidance on this question is lacking, current authority and scholarship suggests that laws regulating the use of genetic information do not apply to epigenetic information. The reasoning rests on a qualitative difference between genetic and epigenetic information. Epigenetic information, at least as is being proposed in the commercial context discussed here, differs from genetic information in that it detects voluntary, non-predetermined conduct relating to states of health that change over the course of life and are possibly reversible, as opposed to detecting latent, immutable genetic instructions over which the insured has no control and for which no disease has yet developed.[39]

Several federal statutes further support this distinction, with language in these code provisions treating genetics and epigenetics as separate categories, implying that if a statute only applies on its face to genetics, it does not apply to epigenetics.[40] Existing scholarship concurs. Rothstein (2009) explained that epigenetic information is distinct from genetic information, and state and federal nondiscrimination laws should be amended to precisely address them as such. Rothstein's understanding that statutes regulating the use of genetic information do not capture epigenetics is widely held. Diemer and Woghiren (2015) argued that "GINA's disregard for phenotype…will have greater bearing in epigenetic protection considering the wider range of variation…that can result from epigenetic alterations," and Dyke, et al (2015) concluded that "GINA probably would not apply to epigenetic information."

Ultimately, legal frameworks will need updating as new technologies move the industry beyond its historical boundaries. Regulators will need to parse the differences in biological and functional properties between epigenetics and genetics to ensure individual information is protected and unfair discrimination does not occur.

4.4 WHAT ARE THE PRIVACY AND CONFIDENTIALITY CONSIDERATIONS OF USING EPIGENETICS FOR UNDERWRITING?

Similar to existing medical information utilized in life insurance underwriting, epigenetic tests can provide sensitive information about an individual's substance use history, health risks, and current health problems, as well as producing potentially identifiable information such as gender and biological age. One study found that certain types of epigenetic information, such as microRNA profiles, can, in fact, be matched to a specific individual with a high

[37] *See, e.g.*, https://mobile.nytimes.com/2014/04/08/science/fearing-punishment-for-bad-genes.html ("'Insurance fears play a big role,' he said. These worries, he added, are spreading to a growing community of people aware of predictive testing for hereditary illnesses like Alzheimer's, breast cancer and colon cancer.").
[38] As of June 17, 2020, HB 1189 has been presented to the Florida Governor for signature.
[39] Shapo, Nat. (2020) *Modern Regulatory Frameworks for Genetic and Epigenetic Underwriting*. Paper submitted for publication.
[40] See, *e.g.,* 42 USC §284g (requiring NIH Director to expand autism activities "including…research in fields including pathology, developmental neurobiology, genetics, epigenetics, pharmacology, nutrition, immunology, neuroimmunology, neurobehavioral development, endocrinology, gastroenterology, and toxicology."); 42 USC §280i (limiting CDC funding if "[t]he center will develop or extend an area of special research expertise (including genetics, epigenetics, and epidemiological research related to environmental exposures), immunology, and other relevant research specialty areas.").

success rate.[41] Another study suggested that certain sensitive information about research participants could be linked to individuals using epigenetic datasets that were being shared online.[42]

As with all personal health information acquired by life insurers, whether through the traditional paramedical examination process (*e.g.,* blood and urine samples), electronic health records, or prescription history records, epigenetic information falls within well-defined boundaries of existing data privacy and security frameworks. These frameworks are designed to protect the confidentiality of consumer information through robust practices that are well established in the industry. An insurance company utilizing epigenetic information would be wise to follow the privacy and security standards laid out by the Health Insurance Portability and Accountability Act (HIPAA), such as implementing appropriate administrative, physical, and technical safeguards for any protected health information (PHI), as well as any other applicable regulations governing data use and security (*e.g.,* California Consumer Protection Act (CCPA), New York's SHIELD Act, and the General Data Protection Regulation (GDPR)). In this sense, epigenetic data can and should be managed and protected like other PHI obtained for underwriting.

4.5 WHAT IS THE POTENTIAL FOR RACIAL BIAS (INTENTIONAL OR UNINTENTIONAL) IN THE USAGE OF EPIGENETIC INFORMATION FOR UNDERWRITING?

Genetic ancestry, while imperfect, has been used as a surrogate measure for race/ethnicity. Any given variant in the genome may be shared by a large number of individuals in a population, so genetic variants must be combined in complex algorithms to estimate a person's ancestral lineage. These sets of genetic variants are sometimes referred to as ancestry informative markers (AIM). AIMs form the basis of a number of consumer genomics products. There is no consensus set of AIMs, but rather different sets created by different groups, each with varying levels of accuracy.[43]

Epigenetic data have been used to roughly identify populations of different ancestral backgrounds.[44] Using epigenetics for this purpose is not as precise as using genetic data, because this phenomenon is partly due to a subset of epigenetic probes that capture the signal of nearby genetic variants that may differ by ancestral lineage. No genetic or epigenetic technology is immune to this possibility, but a simple solution may be to exclude the use of these probes or sequences once identified, even though more precise alternatives can be used to identify the subset of those probes that actually contribute substantially to any bias. That said, an outright ban on the use of specific sequences is neither necessary nor sufficient to guard against such bias, partly due to the abstract yet complex nature of AIMs and partly due to the modest contribution of individual variants to capturing ancestry. Instead, though not currently mandated by law, socially conscious test developers should adopt the onus to demonstrate a lack of differential test performance by racial/ethnic group, a relatively straightforward task that is an extension of current CLIA requirements for examining a number of test performance characteristics, such as accuracy and reliability.

As an example, epigenetic aging, as summary measures of molecular aging and health, may detect health disparities between different ethnic groups.[45] However, in relation to mortality risk, epigenetic aging appears to be consistently associated across racial/ethnic groups, defined as White, Black, Hispanic, and Asian/Pacific Islanders.[46] Thus, the latter check fails to detect any racial bias in the association between epigenetic aging and mortality. But, as is often the case

[41] (Backes et al 2016)
[42] (Philibert et al., 2014)
[43] See *e.g.* "Twins get some 'mystifying' results when they put 5 DNA ancestry kits to the test." CBC, January 2019. https://www.cbc.ca/news/technology/dna-ancestry-kits-twins-marketplace-1.4980976
[44] (Barfield *et al.*, 2014)
[45] (Horvath et al 2016);(Levine et al 2018); (Liu et al 2019)
[46] (Chen et al 2016)

with science, more research is needed, ideally, with ample representation of all racial/ethnic groups. Moving forward, policies must find the appropriate balance that provides societal safeguards without stifling innovation.

The potential for biased outcomes within the underwriting process discussed here is not necessarily unique to epigenetic tests. Like AIMs, names, zip codes, and prevalence of certain traits or diseases may be observed to function as proxies for race, whether intentionally or unintentionally. Simply observing that there are racial differences within these components, and that those differences are associated with existing unequitable health outcomes in society, is not the same as observing racial bias in the end-results of underwriting. Thus, if equitable access to life insurance coverage is sought, a universal and comprehensive approach to combating discrimination and structural barriers is required industry-wide.

4.6 WHAT IS THE STATUS AND ULTIMATE POTENTIAL OF IMPLEMENTING EPIGENETIC INFORMATION IN THE LIFE INSURANCE INDUSTRY?

Creating a frictionless precision underwriting tool that is easy to self-administer and cheap to process could be a game-changing development for the global longevity risk management industry, including life insurance, long-term care, annuities, and pensions. Moreover, epigenetic information could serve as a basis of consumer engagement towards better health and wellness outcomes. Whether the technology can deliver on this promise is subject to additional research and testing, as well as acceptance from regulators and consumers.

In addition, there may be benefits of using epigenetic information that remain hard to quantify. Could a block of in-force business with epigenetic information attached be of greater value in future decades? Perhaps a novel epigenetic biomarker could open new possibilities such as novel risk segmentation categories or even new insurance products. Could there be a way to motivate consumers to improve their health by providing epigenetic-based feedback? All of these considerations and more will need to be thought through as epigenetics and other molecular biotechnologies enter the consumer and life insurance mainstream.

It would be short-sighted to underestimate the pace and veracity of technological change. Knowing that molecular biotechnology is only in its beginning chapters, its impact and future can hardly be foretold. Leading professionals ought, therefore, to stay abreast of the development of these technologies and the implications to the industry.

Section 5: Acknowledgments

The researchers' deepest gratitude goes to those without whose efforts this project could not have come to fruition: the Project Oversight Group and others for their diligent work overseeing questionnaire development, analyzing and discussing respondent answers, and reviewing and editing this report for accuracy and relevance.

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