Exhibit A of Epigenetics White Paper

A. Setting the Stage

Conclusions From the Paper on Epigenetics

The basis for the analysis below is the 2016 paper *DNA methylation-based measures of biological age: meta-analysis predicting time of death*.

The conclusions drawn in that paper about the ability to calculate Extraneous Epigenetic Age Acceleration (EAAA) based on observed blood-cell count compositions, are used as the foundation for a hypothetical insurance situation involving two male lives aged 50.

For purposes of discussion and illustration, these lives will be designated as Male A and Male B respectively.

The facts concerning their biological ages, based on the effects of epigenetic observation, are then used to differentiate the distinct mortality classifications of the two lives.

Distribution of Hazard Ratios

Based on data from the EEAA paper, the normalized distribution of hazard ratio data has the following features, among others:

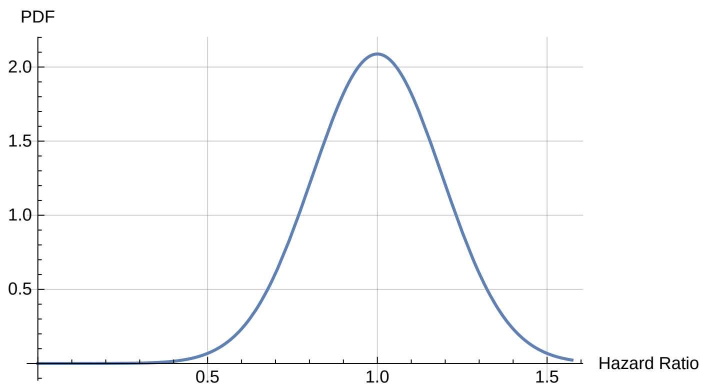
- CDF, Hazard Ratio of 1.00 = 0.5
- CDF, Hazard Ratio of 0.52 = 0.006

Using the above information, the parameters of the distribution can be solved as:

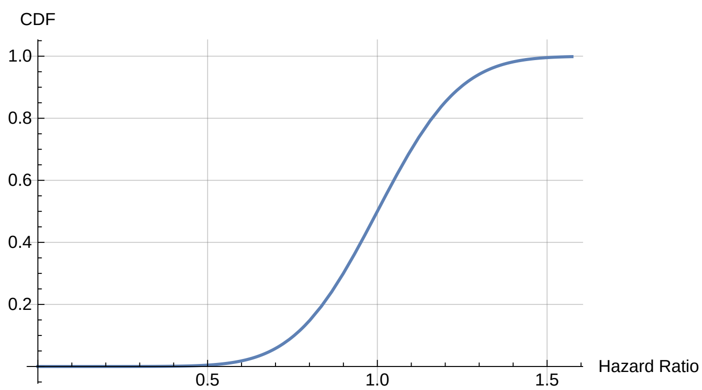
- Mean = 1.00
- Standard Deviation = 0.191072

Relevant tabular and graphical data of this distribution are shown below:

PDF of Distribution



CDF of Distribution



	Hazard Ratio	CDF
Mean − 3 Standard Deviations	0.426785	0.0013499
Mean − 2 Standard Deviations	0.617856	0.0227501
Mean − 1 Standard Deviation	0.808928	0.158655
Mean + 0 Standard Deviation	1.	0.5
Mean + 1 Standard Deviation	1.19107	0.841345
Mean + 2 Standard Deviations	1.38214	0.97725
Mean + 3 Standard Deviations	1.57322	0.99865

Risk Classifications

Imagine that, for a particular insurance company to which both 50-year-olds have applied, the risk classification works as follows:

	Percentage of Standard	Mortality Rate
Preferred Ultimate	0.25	0.00126475
Extra Preferred	0.5	0.0025295
Preferred	0.75	0.00379425
Standard	1.	0.005059
Table A	1.25	0.00632375
Table B	1.5	0.0075885
Table C	1.75	0.00885325
Table D	2.	0.010118
Table E	2.25	0.0113828
Table F	2.5	0.0126475
Table G	2.75	0.0139123

The standard mortality rate for a 50-year old is given as 0.005059, as shown.
In the usual underwriting process, most prospective insureds aged 50 will be assigned this classification and mortality rate. Other persons at this age will be accorded higher or lower mortality rates as depicted in the above table, depending on the risk classification group into which they fall.

At the beginning of the analysis, prior to any epigenetic information, both persons are assumed to fall into the standard class. We will now investigate what happens when the results from epigenetic testing indicate otherwise.

Assuming EEAA Hazard Ratios Are Valid

The mathematical bases that support the contents of this section will be presented in a special section below (‘Support of Conclusions’).

For ease of presentation, it will first be assumed that the conclusions in the EEAA paper referenced above, are valid. In the next section, the validity of the paper’s conclusions will be addressed.

Hazard Ratio for Male A

Male A is shown, after epigenetic observation and examination, to have a hazard ratio of 1.38214 (the reason for the chosen factor will be explained in the special section below). This translates into a mortality rate as follows:

Age	Standard Table Value	Value From Epigenetic Clock
50	0.005059	0.00698549

This person, who was originally thought to be standard, is now seen to be actually closer to a Table B classification. Further implications of this fact are explored in the special section below.

Hazard Ratio for Male B

Male B, on the other hand is shown, after epigenetic observation and examination, to have a hazard ratio of 0.617856 (the reason for the chosen factor will be explained in the special section below). This translates into a mortality rate as follows:

Age	Standard Table Value	Value From Epigenetic Clock
50	0.005059	0.00312877

So a person, originally thought to be standard, is now seen to be actually closer to an Extra Preferred classification. Further implications of this fact are explored in the special section below

Validity of the EEAA Conclusions

The above demonstration is acceptable only if the statistical basis on which it relies (the conclusions from the EEAA study) is valid.

From the paper (under the heading ‘Cox regression models of all-cause mortality’) it is shown that:

- The EEAA approach produces p-values of
  - 7.5×10^{-43} for univariate modeling
  - 3.4×10^{-19} for multivariate modeling
- These were smaller than the corresponding p-values for competing approaches
- The authors of the study therefore considered the resulting conclusions (about the ability of EEAA to accurately predict biological age) to have high statistical significance

B. Special Section: Support of Conclusions

Converting Hazard Ratios Into New Mortality Rates

Definitions and Calculations

The hazard rate (more commonly known as *force of mortality* in actuarial literature) is usually denoted by the symbol μ. By definition, for an attained age x, it is:

$$\mu[x] \equiv \frac{-D[S[x]]}{S[x]}$$

where S[x] is the survival function at attained age x.

From basic actuarial math, we can use the above to derive:

$${}_tp_x = e^{-\int_0^t \mu[x+s]\,ds}$$

where ${}_tp_x$ is the probability that someone aged x will survive t years.

The mortality rate for standard mortality, 0.00509, was derived from a parametrized expression for μ[x], with x in the region of age 50:

$$\mu[x] = 1.56465 \times 10^{-12} + 0.0000414387\, e^{0.0951855\, x}$$

It can readily be verified that under this force of mortality we will obtain

$$\mu[50] = 0.00483429$$

$$p_{50} = 0.994941$$

$$q_{50} = 1 - p_{50} = 0.005059$$

which corresponds with the standard mortality rate with which we began this discussion.

Applying the Hazard Ratios

Male A: Mean Plus 2 Standard Deviations

We will use a factor that is 2 standard deviations greater than the mean of the normalized distribution for the hazard ratio: This amounts to 1.38214.

With a hazard ratio of 1.38214, we obtain new values as follows:

$\mu[x] = 1.38214\left(1.56465\times10^{-12} + 0.0000414387\, e^{0.0951855\,x}\right)$

$\mu[50] = 0.00668167$

$p_{50} = 0.993015$

$q_{50} = 1 - p_{50} = 0.00698549$

It has already been shown that this new mortality rate corresponds to a Table B rating. There are further implications for this change in mortality rate:

First, the mortality rate for standard age 50, is taken from a larger standard (ultimate) table as shown below:

Age	Mortality
42	0.002355
43	0.002594
44	0.00288
45	0.003185
46	0.003503
47	0.003854
48	0.004236
49	0.004641
50	0.005059
51	0.005487
52	0.005935
53	0.006415
54	0.006937
55	0.007505
56	0.008111
57	0.008737
58	0.00936
59	0.009974
60	0.010604
61	0.011276
62	0.012007
63	0.01285
64	0.013848
65	0.015034
66	0.0164
67	0.017917
68	0.019481
69	0.021114
70	0.022988

A cursory survey will reveal that the new mortality, based on the hazard ratio of 1.38214, is tantamount to a standard rate for a person aged approximately 54.

For illustration purposes, we will adopt this view and calculate the actuarial present values of the death benefits over the next 10 years for both age 50 and age 54. To do this, we will assume that:

- The death benefit is a constant 1,000,000 payable at the end of the year of death
- The interest rate applicable to the pricing is 1%

The resulting comparison is shown below:

Actuarial PV, Age 50	Actuarial PV, Age 54	Difference
73 492.7	105 604.	32 111.

For each one million dollar policy that the company is able to correctly classify as Table B, the savings in expected death benefit claims over the next ten years, will be more than $32,000.00 in present value terms.

Male B: Mean Minus 2 Standard Deviations

We will use a factor that is 2 standard deviations less than the mean of the normalized distribution for the hazard ratio: This amounts to 0.617856

With a hazard ratio of 0.617856, we obtain new values as follows:

$$\mu[x] = 0.617856 \left(1.56465 \times 10^{-12} + 0.0000414387\, e^{0.0951855\, x}\right)$$

$$\mu[50] = 0.0029869$$

$$p_{50} = 0.996871$$

$$q_{50} = 1 - p_{50} = 0.00312877$$

It has already been shown that this new mortality rate corresponds to an Extra Preferred rating. Just as with the preceding case, there are further implications for this change in mortality rate:

We will treat the male age 50 mortality to be taken from the same mortality table as used previously:

Age	Mortality
42	0.002355
43	0.002594
44	0.00288
45	0.003185
46	0.003503
47	0.003854
48	0.004236
49	0.004641
50	0.005059
51	0.005487
52	0.005935
53	0.006415
54	0.006937
55	0.007505
56	0.008111
57	0.008737
58	0.00936
59	0.009974
60	0.010604
61	0.011276
62	0.012007
63	0.01285
64	0.013848
65	0.015034
66	0.0164
67	0.017917
68	0.019481
69	0.021114
70	0.022988

A cursory survey will indicate that the new mortality, based on the hazard ratio of 0.5, is tantamount to a standard rate for a person aged approximately 45.

For illustration purposes, we will adopt this view and calculate the actuarial present values of the death benefits over the next 10 years for both age 50 and age 45. To do this, we will again assume that:

- The death benefit is a constant 1,000,000 payable at the end of the year of death
- The interest rate applicable to the pricing is 1%

The resulting comparison is shown below:

Actuarial PV, Age 50	Actuarial PV, Age 45	Difference
73492.7	46351.3	−27141.4

The negative difference of over $27,000 represents a marketing advantage to the life insurance company: It can exploit this difference to charge a lower premium than those competitors who do not have access to information obtained via the epigenetic clock. This will result in increased market share over time.

Lloyd Foster, FSA, MAAA
Director of Analytics,
Avmont, LLC