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REVIEW

An Illustration of the Protective Value of Epigenetics: Using the Alcohol T Score (ATS) in A Population of Known Smokers

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Background.—Previously we have shown that, in theory, a prediction algorithm that incorporates methylation sensitive digital PCR (MSdPCR) assessments of smoking and drinking could predict mortality. But the potential impact of these findings was speculative because limitations of the generalizability and available data from the study cohort.

Objective.—To directly demonstrate the potential financial impact of using an epigenetic mortality index to assess potential applicants based off actual MSdPCR and survival data from a nationally representative cohort.

Methods.—Using actual MSdPCR and survival data from our recent study of the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial, we modeled the survival and financial impact of a 55-year-old male smoker at the 25th, 50th and 75th percentile of Alcohol T Score (ATS) values.

Results.—The likelihood of survival to maturation of 20 years was 86.2%, 80.8% and 74.4%. Using a simplified financial modeling of a 20-year term policy with $500K face value, insuring a client at the 25th percentile, would result in an average of $38,749 and $85,833 more in average net revenue than insuring the individuals at the 50th and 75th percentile.

Conclusions.—Epigenetic survival indices can make financially impactful predictions. Real life pilots of this technology in the underwriting space are in order.

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Smoking and drinking have a profound effect on mortality. Although the rates of these behaviors are thought to be lower in insured populations, their potential for causing mortality slippage remains significant.[1]

The effects of alcohol have been particularly hard to estimate. Specifically, two challenges with respect to alcohol consumption are particularly difficult to address. First, it is often difficult to detect problematic alcohol consumption.[2] Second, it is uncertain as how to quantify the impact of alcohol consumption on mortality.[2,3] Current approaches for addressing these issues are limited. Medical and legal database searches can identify problematic drinkers, but this approach only identifies a fraction of all problem drinkers. Serum biomarkers of alcohol consumption, such as carbohydrate deficient transferrin (CDT), can also be obtained. But this method has limited sensitivity, is confounded by the use of medications such as statins and does not have a published systematic quantitative relationship to mortality.[4]

The use of newly developed epigenetic tools may solve a substantial portion of these problems. Over the past several years, we have introduced two epigenetic tests for smoking and drinking intensity respectively. The assay for smoking (trade name Smoke Signature©) uses methylation sensitive digital polymerase chain reaction (MSdPCR) technology to quantify DNA methylation at cytosine-phospho-guanine (CpG) in the aryl hydrocarbon receptor repressor referred to as cg05575921. Pooled cohort analyses show that it has a 0.985 Receiver Operating Characteristic area under the curve for detecting daily smoking and a dose dependent relationship to smoking intensity.[5] As such, it may be very useful for detecting smoking.

The second tool, the Alcohol T Test (ATS) uses the MSdPCR assessment of four CpG sites specifically sensitive to alcohol to quantify steady state alcohol consumption. The performance characteristics of the ATS have been examined in ten previously published, peer reviewed studies (for review see[6]). In the four studies that included the CDT as a comparator, the ATS consistently outperformed the CDT in predicting alcohol consumption status and alcohol related traits in a gender and race free manner.[6-10]

Despite this evidence, a barrier to the use of the cg05575921 and ATS assays for underwriting has been a lack of systematic understanding of the relationship of their values to survival in the general population. Using proxies of these values in the Framingham Heart Study (FHS), we have shown that they have strong potential to replace or augment current underwriting assessments.[11] But these findings in the FHS were limited by problems with the methylation array data and the limited generalizability of the exclusively White cohort that is largely localized to the Northeast United States.

Conceivably, the use of DNA from a nationally representative cohorts, such as the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial population, could address that shortcoming. The PLCO study was a large randomized controlled trial whose goal was to determine the effects of screening on cancer-related mortality and secondary endpoints in men and women aged 55 to 74. The study enrolled approximately 148,000 individuals at one of ten intake sites in the United States, then followed those subjects for up to 13 years with respect to key outcomes such as occurrence of cancer and mortality.[12]

Recently, as part of a project to develop an epigenetic algorithm for predicting the likelihood of lung cancer, we analyzed the relationship of cg05575921 and ATS values to survival in 494 current or former smokers from the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial. In separate modeling for those who did (n=94) or did not develop lung cancer (n=402), found that the ATS values profoundly predicted the likelihood of survival of individuals in both groups.[13]

In this communication, we reanalyze these data to provide an algorithm for predicting survival agnostic of lung cancer status. We then use that formula to calculate the likelihood of survival hypothetical 55-year-old male smokers who differ with respect to alcohol consumption and illustrate the potential influence of that alcohol consumption on net revenues from $500,000, 20-year term policy.

METHODS

The data used in this study is from Philibert et al *In Revision* and is based on the examination of data and biomaterials from the PLCO Cancer Screening Trial.[12,13] All subjects in the PLCO study provided written informed consent. Institutional Review Board approval was obtained for the entire study, by the National Cancer Institute and individually, at each participating institution.

Coded DNA specimens for each subject were provided by the Frederick National

Laboratory. DNA methylation values for cg05575921 and the ATS were then determined as previously described using methylation sensitive digital polymerase chain (MSdPCR) methodologies.[5,13,14]

The algorithm used in the current study is derived from data from 494 subjects with a history of current or former smoking from the PLCO study for whom both cg05575921 and ATS scores were obtained.[13] The purpose of that larger study is to derive an algorithm that uses cg05575921 methylation to predict the likelihood of developing lung cancer.[15] The study design matches each lung cancer case to 3 controls based on age, sex, ethnicity, smoking status, and smoking history. Because the PLCO study cohort is intentionally overloaded with respect to lung cancer, the model used in this study was adjusted to reflect the 11% likelihood that a smoking subject in the PLCO population would experience lung cancer. A flexible parametric survival model was used to assess ATS in predicting all-cause mortality, adjusting for age, sex, and lung cancer status. Survival probabilities were estimated from spline-based baseline hazard model to compare relative survival at the 25th, 50th, and 75th percentiles of ATS values for a 55-year-old male participant with 11% likelihood of developing lung cancer.[16]

The method for illustrating the potential protective value of the ATS assay was conducted according to the method of Gregory Mills (1991).[17] Key terms for the implementation of that approach were defined for this study as follows: 1) *mortality*, as provided in large, national database as described in Philibert et al., In Revision; 2) *persistency*, for simplicity, we assume equal lapse rates between lighter and heavier drinkers, and between current smokers and former smokers; 3) *underwriting costs*, stipulated as $500 with total additional costs of all epigenetic testing, including administration, at $400 each; 4) *interest rate*, a 5% interest rate, compounded annually, was applied to any payout or cost until the closeout of the portfolio in at Year 20 to reflect the lost revenue that could have been realized from investment; 5) *inflation*, was held at zero; and 6) *time period*, 20 years. Estimate of the annual premium for a 55-year-old white male smoker was obtained from Select Quote on January 27, 2025 (https://life.selectquote.com, Kansas, USA).

Table 1. Key Clinical and Demographic Characteristics of the Subjects Used to Construct the Algorithm.

	Male	Female
N	313	181
Age	62.4 ± 4.8	63.1 ± 5.5
Race*		
White, Non-Hispanic	271	166
Black, Non-Hispanic	17	10
Hispanic	6	2
Asian	17	1
Pacific Islander	1	1
American Indian	1	1
Current Smoker	125	73
Pack Years	45.6 ± 32.2	37.0 ± 29.8
Current Cigs per day		
1-10	13	15
11-20	50	35
21-30	33	16
31-40	24	6
41-60	4	1
61-80	1	-
Developed Lung Cancer	58	34
Cg05575921	60.2% ± 21.3	64.1 ± 19.8
ATS	4.0 ± 3.4	3.4 ± 3.2

* Racial category classifications as provided in the original study.

RESULTS

Key demographic and clinical characteristics of the 494 smokers whose data was used to construct the prediction algorithm are given in Table 1. The age of the subjects ranges from 55 to 74 with the majority (63%) being male. Approximately 12% (57 of 494) of the cohort was non-White. Forty percent of the subjects report current active smoking with the mode for both male and female smoking intensity being between 11-20 cigarettes per day. Males had a greater pack year history of smoking than females (45.6 ± 32.2 vs 37.9 ± 29.8, $p<0.05$). Over the course of the study, 92 of the 494 subjects experienced lung cancer with the proportion of lung cancer cases in each sex in this subsample of the cohort being equal (both 19%). Self-report of subject alcohol intake is not available.

In the survival model, higher age and ATS, male sex, and presence of lung cancer are each associated with increased mortality risk. According to Oken and colleagues, approximately 11% of the subjects with a history of smoking experienced lung cancer over the 13 year follow-up period.[18] Therefore, our survival estimates for 55-year-old male smokers are made with adjustment for a 11% incidence of lung cancer over the 13-year observation period. We also examined the impact of race in the model and found no evidence of an impact on mortality risk.

The 3 expected survival curves of the 55-year-old male smokers at the population mean for smoking (one pack per day) but at different quartiles of ATS values is graphically depicted in Figure 1. The numerical likelihoods of survival for these hypothetical individuals are given in Table 1. As the Figure and Table 1 demonstrate, mortality is lowest in the smoker at the 25th percentile for alcohol use and is highest in the subject at the 75th percentile. Year-to-year mortality begins to exceed one percent in year 12 for the heaviest drinker, but does not exceed one percent per year until year 15 for the lightest drinker.

Table 2 shows the net accumulation of income from premiums expressed at portfolio closeout in Year 20. Because deceased individuals do not pay premiums, the annual premium of $7700 was multiplied by the fractional likelihood of survival, then adjusted for compounding interest at each time point. The extra $400 cost of the ATS at underwriting inception represented a loss of

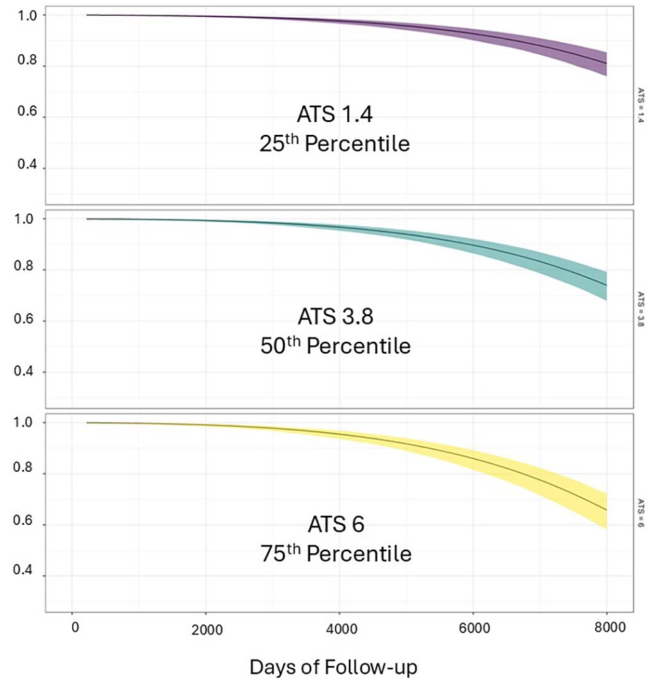

Figure 1. *Survival curves for three 55-year-old male smokers at the 25th, 50th, and 75th percentiles for chronic alcohol consumption. Shaded areas indicate the 95% confidence intervals.*

$1061 to the net revenue for each individual. After adjustment for the cost of initial underwriting and testing, the individual at the 25th percentile of ATS yielded $5599 more in premiums and interest than the individual at the 75th percentile.

Tables 3 and 4 show the expected premiums received and payouts from mortality, respectively, at each time point. These values were calculated by multiplying the year-to-year mortality for each time period by the policy death benefit of $500,000, then adjusted for compound interest. As the Table demonstrates, the average individual at the 50th percentile of ATS would cost $38,749 more in death benefits than the average individual at the 25th percentile. If we make the assumptions listed in the methods, and in addition, assume that 1) an insurer would elect to only insure those smokers who were at the 50th percentile or lower of ATS values, 2) this decision would not have any effects on the number of applicants insured, and 3) the average revenues of those at the 25th and 50th percentile are

Table 2. Survival Probabilities for a 55-year-old male smoker at the 25th, 50th, and 75th percentiles for chronic alcohol consumption.

	ATS 25th Percentile			ATS 50th Percentile			ATS 75th Percentile		
Year	Survival	LCL	UCL	Survival	LCL	UCL	Survival	LCL	UCL
1	0.9997	0.9976	0.9999	0.9995	0.9967	0.9999	0.9993	0.9955	0.9999
2	0.9992	0.9972	0.9997	0.9988	0.996	0.9996	0.9984	0.9944	0.9995
3	0.9985	0.9963	0.9994	0.9979	0.9948	0.9991	0.997	0.9927	0.9987
4	0.9975	0.9948	0.9988	0.9964	0.9927	0.9982	0.995	0.9901	0.9974
5	0.9962	0.9931	0.998	0.9946	0.9903	0.997	0.9925	0.9868	0.9958
6	0.9952	0.9917	0.9973	0.9932	0.9883	0.996	0.9906	0.9841	0.9945
7	0.9914	0.9859	0.9948	0.9878	0.9806	0.9924	0.983	0.9732	0.9894
8	0.9897	0.9833	0.9936	0.9852	0.9772	0.9905	0.9795	0.9684	0.9867
9	0.9859	0.9781	0.9909	0.9798	0.9697	0.9866	0.9721	0.9583	0.9814
10	0.9821	0.9729	0.9882	0.9745	0.9623	0.9824	0.9647	0.9483	0.9758
11	0.9774	0.9662	0.985	0.9678	0.9539	0.9773	0.9555	0.9361	0.9688
12	0.9707	0.9566	0.9801	0.9583	0.941	0.9702	0.9425	0.9193	0.9586
13	0.9633	0.9467	0.9744	0.9478	0.9273	0.9619	0.9281	0.9008	0.9476
14	0.9556	0.937	0.9687	0.9371	0.9135	0.9535	0.9136	0.8826	0.9362
15	0.9449	0.923	0.9605	0.922	0.8943	0.942	0.8932	0.8569	0.9199
16	0.9319	0.9059	0.9508	0.9039	0.8714	0.9278	0.8689	0.8274	0.9005
17	0.9187	0.8888	0.9403	0.8856	0.8485	0.9136	0.8446	0.797	0.8814
18	0.9024	0.8676	0.9276	0.8631	0.8205	0.8958	0.8149	0.7604	0.8588
19	0.8848	0.8459	0.9143	0.8392	0.7917	0.8769	0.7837	0.7232	0.834
20	0.862	0.817	0.8966	0.8083	0.7567	0.8513	0.7438	0.6783	0.8008

the averages for the average revenue in the lower half and in the total distribution of ATS values, respectively, this would infer a protective value of $14,204 per test.

DISCUSSION

In this straightforward illustration of the potential value of the ATS that uses data from a nationally representative group of current and former smokers, we showed the effect of sustained alcohol consumption on mortality and the impact of this alcohol consumption in a simplified life insurance scenario. But before considering these findings, it is important to consider key limitations of this study. First, our data are informative only for individuals applies between the ages of 55 and 74 in the United States. Second, even though laboratory testing is not usually used at this face value of a policy (and it would not have been required according to the Select Quote salesperson to whom we spoke),[1] if our example was generalized and applied to a real population, it is likely that some of heavier alcohol consumption would have been detected by the underwriting process. Third and finally, the characteristics of self-declared smokers in this nationally representative population may differ from those applying for life insurance.

Understanding the degree of excess mortality or "mortality slippage" in blocks of in force policies due to factors such as alcohol consumption is difficult for several reasons. First, because estimates of the effects of excessive alcohol consumption on mortality are largely based on self-report data, they are likely underestimates.[19] Second, there is considerable debate in the field as to the relationship between alcohol use and mortality. Specifically, the assertion that low levels of alcohol (eg, 1-2 drinks per day) are protective is controversial.[20] Third, even when viewed most favorably, tests

Table 3. Total value of premiums paid at policy maturation adjusted for the value accrual from investment at 5%.

		Income from Premiums					
Year	Compound Factor	ATS 25^{th}	Total at Maturity	ATS 50^{th}	Total at Maturity	ATS 75^{th}	Total at Maturity
1	2.653298	$6,800	$18,042	$6,800	$18,042	$6,800	18042.42
2	2.52695	$7,698	$19,452	$7,696	$19,448	$7,695	19443.9
3	2.406619	$7,694	$18,516	$7,691	$18,509	$7,688	18501.32
4	2.292018	$7,688	$17,622	$7,684	$17,611	$7,677	17595.6
5	2.182875	$7,681	$16,766	$7,672	$16,748	$7,662	16724.09
6	2.078928	$7,671	$15,947	$7,658	$15,921	$7,642	15887.69
7	1.979932	$7,663	$15,172	$7,648	$15,142	$7,628	15102.17
8	1.885649	$7,634	$14,395	$7,606	$14,342	$7,569	14272.67
9	1.795856	$7,621	$13,686	$7,586	$13,623	$7,542	13544.62
10	1.710339	$7,591	$12,984	$7,544	$12,904	$7,485	12802.18
11	1.628895	$7,562	$12,318	$7,504	$12,223	$7,428	12099.74
12	1.551328	$7,526	$11,675	$7,452	$11,561	$7,357	11413.66
13	1.477455	$7,474	$11,043	$7,379	$10,902	$7,257	10722.26
14	1.4071	$7,417	$10,437	$7,298	$10,269	$7,146	10055.66
15	1.340096	$7,358	$9,861	$7,216	$9,670	$7,035	9427.198
16	1.276282	$7,276	$9,286	$7,099	$9,061	$6,878	8777.805
17	1.215506	$7,176	$8,722	$6,960	$8,460	$6,691	8132.381
18	1.157625	$7,074	$8,189	$6,819	$7,894	$6,503	7528.522
19	1.1025	$6,948	$7,661	$6,646	$7,327	$6,275	6917.89
20	1.05	$6,813	$7,154	$6,462	$6,785	$6,034	6336.215
			$258,927		**$256,441**		**$253,328**

such as the ATS and CDT are not perfect indicators of alcohol consumption. Therefore, developing a comprehensive understanding of alcohol may be a slow undertaking.

Nevertheless, these data strongly suggest that developing that understanding could have significant impact on addressing mortality slippage. In this idealized scenario, the net difference to the portfolio at 20 years for the 25^{th} percentile smoker as compared to the 50^{th} and 75^{th} percentile smoker is $38,749 and $85,833, respectively. This difference in portfolio performance is largely due to the differences in death benefit costs from the differential mortality of two levels of drinking. Still, a pitfall of simple models is that they understate the true complexity of the populations they seek to model. Only examinations of actual client biomaterial and outcomes can determine whether the conclusions drawn from this modeling are reasonably accurate.

In this example, we specifically chose the $500K face value because the greatest proportion of mortality slippage is observed in policies with face values between $500K-$1M.[1] However, this idealized example is only for illustrating the impact of excessive alcohol use on mortality slippage and testing typically is not used in these cases.

So then, what are the real-life potential use cases for this technology? We believe that depending on the price point of the assays, there are three potential use case scenarios. The first, and most obvious use case, is for the assessment of policies of greater than $10M. For policies of that magnitude, full underwriting procedures are universally employed, and the potential protective cost of the assay would outweigh virtually any charge. The second use case would be an additional lab test as part of the underwriting process. A challenge to this application

Table 4. The average expected payout of death benefits at each time point, adjusted for value gained by investment for 55-year-old male smokers at three quartiles of chronic drinking intensity.

		Fractional Payout from Mortality					
Year	Compound Factor	ATS 25th	Total at Maturity	ATS 50th	Total at Maturity	ATS 75th	Total at Maturity
1	2.653298	$150	$398	$250	$663	$350	$929
2	2.52695	$250	$632	$350	$884	$450	$1,137
3	2.406619	$350	$842	$450	$1,083	$700	$1,685
4	2.292018	$500	$1,146	$750	$1,719	$1,000	$2,292
5	2.182875	$650	$1,419	$900	$1,965	$1,250	$2,729
6	2.078928	$500	$1,039	$700	$1,455	$950	$1,975
7	1.979932	$1,900	$3,762	$2,700	$5,346	$3,800	$7,524
8	1.885649	$850	$1,603	$1,300	$2,451	$1,750	$3,300
9	1.795856	$1,900	$3,412	$2,700	$4,849	$3,700	$6,645
10	1.710339	$1,900	$3,250	$2,650	$4,532	$3,700	$6,328
11	1.628895	$2,350	$3,828	$3,350	$5,457	$4,600	$7,493
12	1.551328	$3,350	$5,197	$4,750	$7,369	$6,500	$10,084
13	1.477455	$3,700	$5,467	$5,250	$7,757	$7,200	$10,638
14	1.4071	$3,850	$5,417	$5,350	$7,528	$7,250	$10,201
15	1.340096	$5,350	$7,170	$7,550	$10,118	$10,200	$13,669
16	1.276282	$6,500	$8,296	$9,050	$11,550	$12,150	$15,507
17	1.215506	$6,600	$8,022	$9,150	$11,122	$12,150	$14,768
18	1.157625	$8,150	$9,435	$11,250	$13,023	$14,850	$17,191
19	1.1025	$8,800	$9,702	$11,950	$13,175	$15,600	$17,199
20	1.05	$11,400	$11,970	$15,450	$16,223	$19,950	$20,948
			$92,006		**$128,269**		**$172,240**

would be the current costs of epigenetic testing. Right now, these costs are much higher than the typical laboratory tests offered by the major laboratory testing companies. However, as the frequency of these tests grows and the testing process becomes automated, these costs will decrease.

However, it is the third use case that may be potentially transformational to the life insurance community. In this scenario, the tests would be given to those offered policy policies on a tentative basis pending epigenetic testing. Whereas this approach would lead to greater number of policies not taken, if the approach allowed for more favorable rates than could otherwise be obtained on the market, it could lead to retention of those who are at lower risk and a shift of higher risk individuals who would avoid this testing to other carriers. Fortunately, because both the ATS and the cg05575921 assay can be performed on saliva DNA, this could allow overnight delivery of remotely monitored saliva samples that would facilitate rapid turnaround of samples necessary for rapid decision making. Alternatively, remotely monitored sampling of blood, such as that achieved by Quest using the Tasso system[21] would allow collection of blood samples that also could be used for these and other testing purposes as well. Finally, in what would eliminate the need for video monitored sampling techniques, a carrier could pair its efforts with a national chain, such as Walmart, with a physical presence throughout the count. By having the blood or saliva sampling kits ready for use, the commercial partner could verify the applicant's identity, supervise the sample collection and send the sample directly to the lab thus expediting the testing process and ensuring chain of custody.

These data do not speak to the value of using the ATS in younger smokers. Because the natural mortality of younger subjects would be lower, the net differences in revenue between the quartiles would be lower. Still, because of recent findings that suggest greater than expected mortality in those men between the ages of 35 to 45,[22] we speculate that these differences could be substantial and note that they are also strongly dependent on the face value of the policy. Therefore, even with lower levels of mortality, the net differences in revenue between the ATS quartiles at higher face values of the policy could be substantial.

A final question is "*What is the value of ATS in a non-smoking population?*" It is well established that heavy drinking is less common is those who do not smoke than among those who do smoke, and only 15% of American adults are current smokers.[23-26] As of yet, we have not directly determined the relationship of ATS levels to survival to those who do not smoke in the PLCO population. Given prior epidemiological evidence between heavy alcohol consumption and mortality,[27] we are optimistic that there will be a strong relationship but note that the value of a test will ultimately be dependent on the characteristics of the applicant pool being surveyed.

In summary, we report that models based on nationally representative data suggest that alcohol may have a significant, perhaps previously not fully appreciated impact on the survival of insured smokers and suggest that large-scale, real-world tests of this technology could have significant implications for medical underwriting procedures.

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Statement of Conflict: *Dr. Philibert is the Chief Executive Officer of Behavioral Diagnostics. The use of cg05575921 to assess smoking status is covered by existing and pending patents including US Patents 8,637,652 and 9,273,358. Similarly, the use of DNA methylation to assess alcohol is covered by existing and pending patents including European Union Patent 3149206.*

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