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# Assessing a predictive model for reflex hepatitis B testing

**White Paper – April 2024**

**Optimum Re Life Research and Development – Biometric Risk**

# Summary

According to 2019 GBD estimates, about 15 out of 10,000 deaths in the US and Canada are related to hepatitis B.

Chronic hepatitis B presents a challenge for life underwriting because it is asymptomatic and conventional reflex rules for testing are not effective.

ExamOne® recently sought to produce a better reflex rule for hepatitis B screening in life insurance using predictive modelling. In this paper, we evaluate the performance of the ExamOne model in comparison to conventional reflex rules that are solely based on the results of liver function tests.

Our analysis of the ExamOne model suggests that prediction modeling may offer a more fruitful reflex rule for hepatitis B testing.

## Layout

# 1. Hepatitis B

## 1.1 Background

Hepatitis B is a viral infection of the liver which could be acquired at birth through mother-to-child transmission, or later in life through contact with contaminated body fluids such as blood and semen [1]. While most individuals who get infected by the hepatitis B virus (HBV) will clear the virus and recover completely, some will experience a chronic destruction of liver tissues that could lead to serious medical conditions including liver cirrhosis, cancer, and death.

## 1.2 Epidemiology

WHO reports that there are about 296 million HBV carriers in the world and 820,000 annual deaths are attributable to hepatitis B [2]. The prevalence of hepatitis B varies widely across countries, ranging from 0.1% - 2% in most developed countries, to 6% - 16% in developing countries [3]. In the US, the prevalence is around 0.4% while in Canada it is about 0.8%. According to 2019 GBD estimates, about 15 out of 10,000 deaths in the US and Canada are related to hepatitis B, and male carriers have a higher mortality rate than female carriers [4]. There is no definitive treatment for chronic hepatitis B, but new infections and premature deaths can effectively be prevented through vaccination, prenatal care, safe sex, and screening.

## 1.3 Hepatitis B Screening

The CDC estimates that about 2 out of 3 HBV carriers in the US are unaware of their hepatitis B status. This is because the disease often sets in and progresses without any specific symptoms [5]. Screening is therefore crucial to reduce disease transmission and progression. Current recommendations in the US encourage all adults to be screened at least once in their lifetime, and all pregnant women to be screened during each pregnancy.

# 2. Predictive modeling for hepatitis B risk

## 2.1 The challenge with hepatitis B screening in life insurance

When a prospective client applies for a life insurance product, the insurance company covers all the expenses required by the application process including lab testing. Systematic screening for hepatitis B would be expensive and have a low yield for insurance companies, especially in developed countries where the prevalence of Hepatitis B is low. In this context, it may be cost saving to apply a selection criterion, also known as a reflex rule, to identify high risk applicants who are most likely going to be detected with a screening test. Most conventional reflex rules imply testing applicants with concentration of liver enzymes in blood above a certain threshold. Unfortunately, using the concentration of liver enzymes is low yield as laboratory data show that liver enzymes are weak predictors of hepatitis B carrier status [6]. This implies that insurance companies waste significant resources testing a large proportion of applicants that are flagged by conventional reflex rules. An effective reflex rule will improve the cost/benefit of testing for hepatitis B, as well as enhance early diagnosis and clinical management of applicants with hepatitis B.

## 2.2 The ExamOne reflex model for hepatitis B testing

ExamOne, a major provider of insurance lab testing in the US and Canada, built a statistical model to provide a more accurate reflex rule for hepatitis B detection using data from laboratory investigations in the insurance context. The data analyzed included over 50,000 subjects, most of which were systematically tested for hepatitis B without any prior selection criteria. The development dataset was international with a vast majority of subjects being Canadian. The screening test used was based on the detection of the hepatitis B surface antigen which is a marker of chronic hepatitis B infection.

The method used to build the model was logistic regression with stepwise forward selection. 16 out of 35 candidate predictors performed well enough to be retained in the final model, namely; age, sex, height, pulse rate, pulse pressure, systolic blood pressure, body mass index, serum albumin-protein ratio, urine protein-creatinine ratio, high density lipoprotein, alanine transaminase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), serum creatinine, cholesterol, bilirubin, and alkaline phosphatase.

## 2.3 Comparing the ExamOne model to conventional reflex rules.

In the rest of this paper, we will explore a dataset provided by ExamOne and use this to assess the performance of their predictive model in comparison with the conventional practice of categorizing hepatitis B risk with respect to arbitrary thresholds of liver enzyme concentration in blood.

To assess distribution, we grouped variables into deciles, that is, 10 groups of approximately equal sizes. The dataset provided by ExamOne included most of the data they used in the model development dataset. ExamOne built a prediction model to generate hepatitis B risk scores for each subject. We used these risk scores to assess model performance.

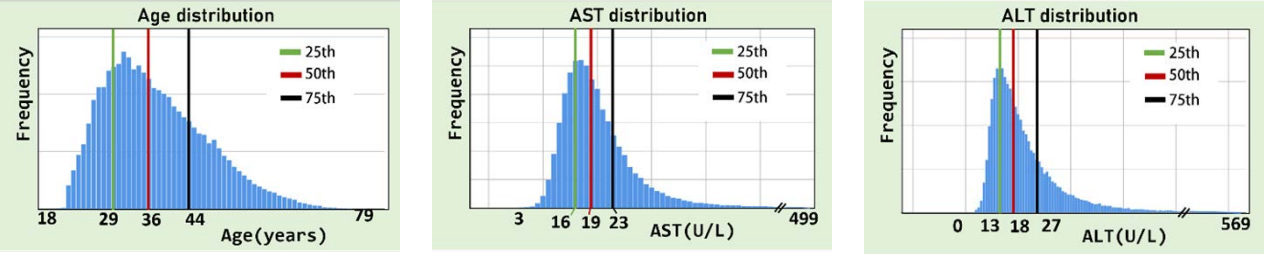
## i. Describing the dataset

Table 1: Demographics and summary liver function test values in dataset.

| Variable | Total | Male | Female |
|---|---|---|---|
| **Total** | 62,658 | 34,171 (54.5%) | 28,487 (45.5%) |
| **Country** | | | |
| Canada | 59,430 (94.8%) | 31,734 (53.4%) | 27,696 (46.6%) |
| USA | 2,086 (3.3%) | 1,683 (80.7%) | 403 (19.3%) |
| Others | 1,142 (1.8%) | 754 (66.0%) | 388 (34.0 %) |
| **Mean age** (years) | | | |
| In dataset | 37.3, SD: 10.2 | 38.0, SD: 10.4 | 36.4, SD: 9.9 |
| In cases with hep B | 39.2, SD: 9.5 | 39.6, SD: 9.3 | 38.6, SD: 9.7 |
| **ALT (IU/L)** | | | |
| In dataset | 22.8, SD: 16.0 | 28.0, SD: 17.6 | 16.5, SD: 10.7 |
| In cases with hep B | 27.9, SD: 21.0 | 31.1, SD: 19.31 | 22.9, SD: 22.6 |
| **AST (IU/L)** | | | |
| In dataset | 20.5, SD: 9.4 | 22.8, SD: 10.3 | 17.8, SD: 7.2 |
| In cases with hep B | 22.9, SD: 9.9 | 24.2, SD: 9.1 | 20.8, SD: 10.8 |
| **Hepatitis B cases** | 597 (1.0%) | 364 (1.1%) | 233 (0.8%) |

# 2. Predictive modeling for hepatitis B risk (cont'd)

**Figure 1: Summary distribution of age and liver function test values in dataset.**




Out of 62,658 subjects, 94.8% resided in Canada, 3.3% in the US, and 1.8% in other countries or territories (table 1). Male and female applicants were almost equally represented with a mean age of 37.3 years. 1% of the sample had a positive hepatitis B test. The sample distribution for age shows that fewer elderly subjects were represented, while ALT and AST distributions were skewed to the right by few extreme values which we kept in the analysis.

## ii. Exploring the distribution of hepatitis B in the sample N = 62,658

Table 2: Prevalence of hepatitis B across countries

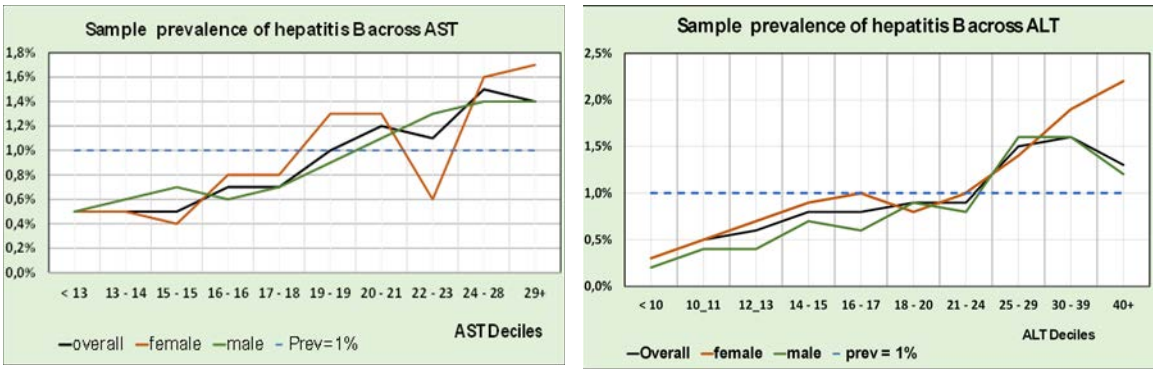
| Hepatitis B prevalence | Overall | Male | Female |
|---|---|---|---|
| **In dataset** | 597 (1.0%) | 364 (1.1%) | 233 (0.8%) |
| **Canada** | 543 (0.9%) | 326 (1.0%) | 217 (0.8%) |
| **USA** | 15 (0.7%) | 12 (0.7 %) | 3 (0.7 %) |
| **Others** | 39 (3.4%) | 26 (3.4%) | 13 (3.4%) |

Table 3: Prevalence of hepatitis B across age groups

| Age group | Count in age group | Percentage in dataset | Hepatitis B status | |
|---|---|---|---|---|
| | | | Negative | Positive |
| 20 - 24 | 4,640 | 7.48% | 4,626 (99.7%) | 14 (0.3%) |
| 25 - 29 | 11,032 | 17.78% | 10,943 (99.2%) | 89 (0.8%) |
| 30 - 34 | 12,853 | 20.72% | 12,751 (99.2%) | 102 (0.8%) |
| 35 - 39 | 10,831 | 17.46% | 10,706 (98.8%) | 125 (1.2%) |
| 40 - 44 | 8,566 | 13.81% | 8,471 (98.9%) | 95 (1.1%) |
| 45 - 49 | 6,374 | 10.28% | 6,289 (98.7%) | 85 (1.3%) |
| 50 - 54 | 4,226 | 6.81% | 4,172 (98.7%) | 54 (1.3%) |
| 55 - 59 | 2,251 | 3.63% | 2,232 (99.2%) | 19 (0.8%) |
| 60 - 64 | 1,206 | 1.94% | 1,199 (99.4%) | 7 (0.6%) |
| 65 - 69 | 499 | 0.80% | 495 (99.2%) | 4 (0.8%) |
| 70+ | 150 | 0.24% | 147 (98.0%) | 3 (2.0%) |
| **Total** | **62,628** | **100%** | **62,031 (99.0%)** | **597 (1.0%)** |

# 2. Predictive modeling for hepatitis B risk (cont'd)

**Figure 2: Prevalence of hepatitis B across ALT and AST values in dataset**




The prevalence of hepatitis B was highest (3.4%) in countries outside the US and Canada, but this represented just 39 cases (table 2). Canadian subjects who represented 94.8% of the sample, had a prevalence of 0.9%, and contributed 543 cases of hepatitis B out of 597 in the dataset. Sex appeared to be associated with the prevalence of hepatitis B with more cases observed in males (1.1% prevalence in males versus 0.8% in females). Table 3 shows that age alone was weakly correlated with hepatitis B as prevalence fluctuates across ages.

Figure 2 illustrates a consistent rise in the prevalence of hepatitis B as the level of liver enzymes increases, suggesting that there is some correlation between the concentration of liver enzymes and the prevalence of hepatitis B. However, only a small proportion of the sample would be categorized as having a high level of liver enzymes based on laboratory thresholds, and the frequency of hepatitis B in those with high levels of liver enzymes is very small compared to that in those with normal levels of liver enzymes (10 hepatitis B cases had elevated AST level compared to 587 that did not and 48 hepatitis B cases had elevated ALT levels compared to 549 that did not, using ExamOne physiologic thresholds of 33 for AST and 45 for ALT).

# 2. Predictive modeling for hepatitis B risk (cont'd)

## iii. Assessing the diagnostic performance of different reflex rules

Table 4: Predictive performance of various reflex rules

| Reflex Rule | AUROC |
|---|---|
| Model Risk scores | 0.809 |
| ALT concentration | 0.612 |
| AST concentration | 0.607 |
| AST_41_ALT_45 | 0.512 |
| AST_41_ALT_40 | 0.521 |
| AST_41_ALT_35 | 0.528 |
| AST_36_ALT_45 | 0.510 |
| AST_36_ALT_40 | 0.519 |
| AST_36_ALT_35 | 0.526 |
| AST_31_ALT_45 | 0.516 |
| AST_31_ALT_40 | 0.521 |
| AST_31_ALT_35 | 0.528 |

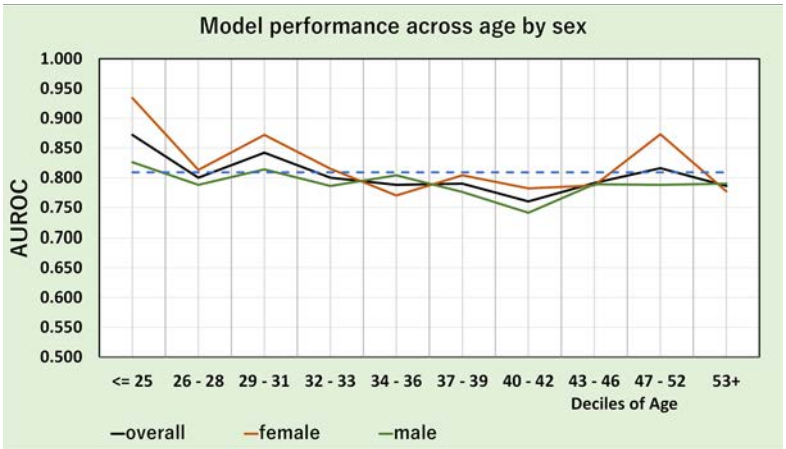



**Figure3: predictive performance of ExamOne model across age groups by sex**

We considered 8 common combinations of ALT and AST thresholds to represent conventional reflex rules in the life insurance industry. For example, the rule labelled "AST_33_ALT_45" means that those with either AST above 33 IU/L or ALT above 45 IU/L are classified as being at high risk for hepatitis B.

To measure model performance, we used the AUROC which stands for "area under the receiver operating characteristic curve". It summarizes model performance with a single number on a scale of 0.5 to 1 where 0.5 means that the model is useless, and its predictions are no better than a coin toss, while a score of 1 would mean that the model's predictions are perfect.

In the dataset, the AUROC was 0.809 for the ExamOne model, while the AUROCs for ALT and AST were 0.612 and 0.607 respectively (table 4). This strongly suggests that the ExamOne model has a greater predictive value than ALT or AST levels. All conventional rules based on ALT and AST values had an AUROC slightly higher than 0.5, indicating little or no accuracy in predictions. Figure 3 shows that the ExamOne model performs reasonably well in both men and women across deciles of age. There was no evidence of any meaningful changes in model performance across deciles of age.

# 2. Predictive modeling for hepatitis B risk (cont'd)

**Figure 4: Comparative assessment of the performance of reflex rules**

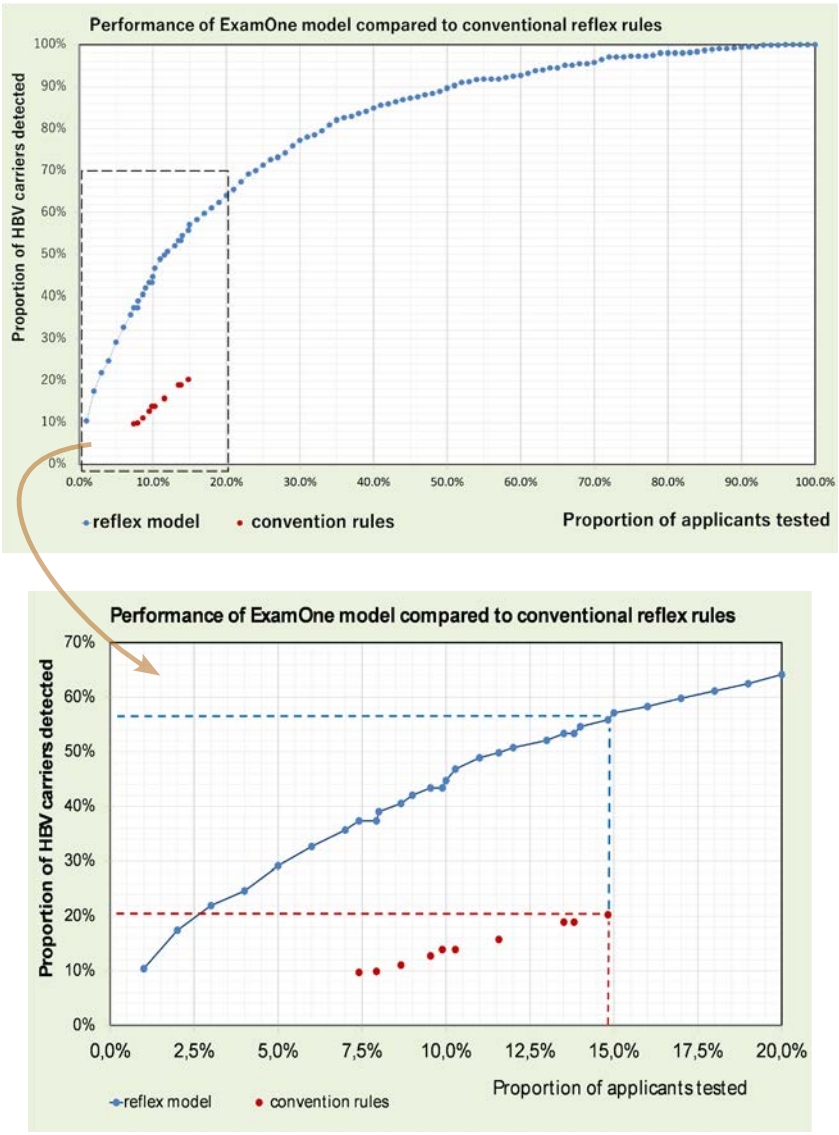



Figure 4 illustrates a practical implication of model performance to life underwriting. For each reflex rule considered in this paper, it matches the proportion of applicants flagged as being high risk and tested for hepatitis B (horizontal-axis), to the proportion of true positive cases detected (vertical-axis). For instance, if a company is willing to test 15% of all its applicants, the conventional reflex rule which corresponds to this (AST_41_ALT_35) would lead to the identification of about 20% of hepatitis B cases (120 cases out of 597 in dataset), whereas if the ExamOne model was applied, the company would have identified about 55% of hepatitis B cases (329 cases out of 597).

Assuming model validity, the above data could be summarized as follows:

- For a prevalence of hepatitis B of 1%, 1000 applicants will contain 10 cases of hepatitis B.
- If we suppose that an insurance company is willing to test 150 individuals out of 1000 applications:
  - › The ExamOne model will enable the company to identify about 6 out of the 10 cases with 150 tests.
  - › Conventional reflex rules will enable the company to identify less than 2 out of 10 with 150 tests.

## 3. Some limitations of the model

1. The model was not trained and validated as standard practice in prediction modelling would recommend, and the data used in this paper was almost the same as the training dataset.

2. The data was principally Canadian. We may assume internal validity for the Canadian and American populations, but the applicability of the model out of these countries is uncertain.

3. The dataset contained a small sample of applicants above 65 years of age, making observations on model performance uncertain in this subgroup. However, we have not observed any meaningful change in model performance with respect to age.

## 4. Conclusion

Chronic hepatitis B may considerably affect mortality but life underwriting often misclassifies the risk of most applicants with this illness. This is because cases are usually asymptomatic and conventional reflex rules for hepatitis B screening are inaccurate. Using ExamOne's prediction model may lead to a major improvement in this regard.

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**OPTIMUM RE INSURANCE COMPANY**

1345 River Bend Drive, Suite 100
Dallas, TX 75247, U.S.A.
+1 214 528-2020
+1 214 528-2777

www.optimumre.com
www.optimumre.com/linkedin