positive effects existed for patients with and without hypertension (Figure 2). The results indicate that the P4P program works for patients with or without MCCs.

Although the effects of various P4P programs in Taiwan and other countries show different effects, the findings from Professor Cheng's team provide robust evidence for the NHI's P4P program for diabetes care. The findings support a further expansion of the coverage rate of the P4P program for diabetes care by the NHI Administration and encourage continuous improvement in healthcare outcomes for patients with MCCs in Taiwan. The success of Taiwan's P4P program for diabetes care might be a valuable example for health policymakers in other countries.

References

1. Chi-Chen Chen and Shou-Hsia Cheng, (2016). Does pay-for-performance benefit patients with multiple chronic conditions? Evidence from a universal coverage health care system. *Health Policy and Planning*, 31(1), 83-90. DOI: 10.1093/heapol/czv024.

2. Shou-Hsia Cheng*, Tai-Ti Lee, Chi-Chen Chen*, (2012). A longitudinal examination of a pay-for-performance program for diabetes care: Evidence from a natural experiment. *Medical Care*, 50(2), 109-116. DOI: 10.1097/MLR.0b013e31822d5d36

3. Tai-Ti Lee, Shou-Hsia Cheng, Chi-Chen Chen, and Mei-Shu Lai, (2010). A pay for performance program for diabetes care in Taiwan: a preliminary assessment. *American Journal of Managed Care*, 16(1), 65-69.

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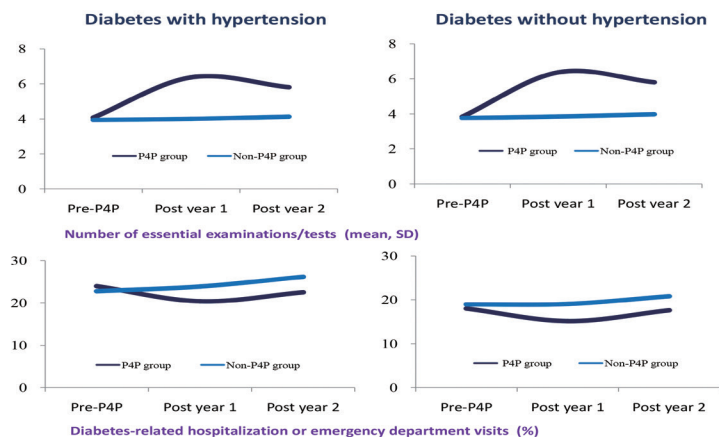Institute of Health Policy and Management
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Figure 2. The effects of the P4P program for diabetes care on recommended care provisions and diabetes-related hospitalizations or emergency department visits for patients with and without hypertension.

Risk of hepatitis B virus-induced hepatocellular carcinoma: the influence of the progressive accumulation of viral mutations during chronic infection

NTU long-term follow-up study used viral whole-genome sequencing to identify a temporal mutation profile that can indicate which patients with HBV will develop HCC

Chronic hepatitis B virus (HBV) infection is a major cause of hepatocellular carcinoma (HCC), accounting for approximately 50% of global HCC cases; the greatest burden of HBV-induced HCC is found in Southeast Asia. Although chronic carriers of HBV have a 20-fold increase in HCC risk, rates of progression to HCC differ substantially among HBV carriers and are thought to be affected by virus-host interactions.

HCC develops via the progression of hepatitis B through a series of stages, and the virus may be continuously changing due to immune selection pressure. The detection of naturally occurring HBV mutations has important implications for antiviral therapy and hepatic disease progression. Previous studies on HCC-related variations and mutations in the HBV genome have been limited to the genotype level or to particular regions of the viral genome. Most of these studies involved a small number of patients and utilized a retrospective study design; in such contexts, the temporal sequence of mutations leading to HCC could not be established.

In September 2016, a research team led by Professor Ming-Whei Yu at the Graduate Institute of Epidemiology and Preventive Medicine published a study in *Hepatology* describing how a temporal mutation profile of HBV that affects progression from a chronic HBV carrier state to HCC was identified via analysis of the whole viral genome.

In a cohort of 4,841 patients with HBV, the research team performed viral genome sequencing in blood obtained <1 to 20 years prior to diagnosis from 117 patients who developed HCC and 118 patients who did not develop HCC. The results revealed a set of 10 HBV-single nucleotide polymorphisms (SNPs) associated with an increased risk of HCC that had odds ratios ranging from 1.89 to 8.68 after accounting for HBV genotype. Further analysis of 163 GenBank HBV-HCC sequences from 9 Asian regions provided additional supportive evidence for associations between these ten viral SNPs and HCC.

The prevalence of these HCC-related viral SNPs and the corresponding mutation score significantly increased over time as diagnosis of HCC approached. When compared with a mutation score of 0, mutation scores of 1, 2, 3, and ≥4 were associated with adjusted odds ratios for developing HCC of 2.17, 4.21, 8.15, and 19.15, respectively. For predicting short-term HCC risk, mutation score outperformed HBV DNA levels, viral genotype, and various combinations of other risk factors, with high accuracy within 4.5 years prior to the clinical onset of HCC (area under the curve=0.83–0.89; sensitivity=72.7–94.1%; specificity=58.3–70.5%).

This analysis of the whole viral genome highlights the importance of identifying and tracking viral mutations for monitoring hepatitis B progression and achieving the early detection of HCC. A mutation score may also be useful as a biomarker for predicting short-term risk of HCC.

Reference
Feng-Yu Sung, Chia-Ying Lan, Chi-Jung Huang, Chih-Lin Lin, Chun-Jen Liu, Pei-Jer Chen, Shi-Ming Lin, Ming-Whei Yu, (2016). Progressive accumulation of mutations in the hepatitis B virus genome and its impact on time to diagnosis of hepatocellular carcinoma. *Hepatology*, 64(3), 720-731. doi: 10.1002/hep.28654.

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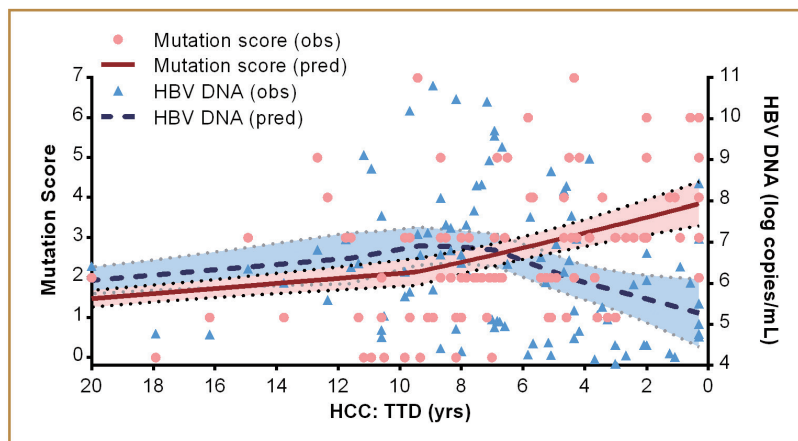*yumw@ntu.edu.tw*

Figure 1. Changes in mutation score and HBV DNA level as a function of time to diagnosis (TTD) (adapted from *Hepatology*, 2017).