DEVELOPMENT AND EVALUATION OF PERSONALIZED RISK ASSESSMENTS FOR OSTEOPOROTIC PATIENTS

by

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CERTIFICATE OF ORIGINAL AUTHORSHIP

I, Le Phuong Thao HO, declare that this thesis is submitted in fulfilment of the requirements for the award of Doctor of Philosophy in the School of Biomedical Engineering at the University of Technology Sydney.

I also declare that the intellectual content in this thesis is the product of my own work, except to the extent that assistance from others in the project's design and conception or in style, presentation and language expression is acknowledged. In addition, I certify that all information sources and literature used are indicated in the thesis.

The work in this thesis has not previously been submitted for a degree, nor has it been submitted as part of the requirements of a degree, at any other academic institution, except as fully acknowledged within the text.

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ABSTRACT

Osteoporosis is a skeletal disease characterized by reduced bone strength and deterioration in bone microstructure, leading to increased risk of fragility fracture. Bone strength is mainly determined by bone mineral density (BMD). The variation in BMD is partly determined by genetic factors. An individual's risk of fracture is determined by the individual's genetic structure and environmental exposures. While several genetic variants associated with BMD have been identified, the contribution of these variants to fracture risk prediction has not been well-documented. In this thesis, I sought to (i) construct an osteogenomic profile from BMD-associated genetic variants; (ii) assess the association between the profile and fracture risk and bone loss; (iii) determine the clinical utility of the osteogenomic profile in terms of fracture risk assessment; and (iv) improve the accuracy of hip fracture prediction in postmenopausal women by using artificial neural network approach.

The work in this thesis was based on the Dubbo Epidemiology Osteoporosis Study, which is designed as a population-based longitudinal prospective cohort investigation that involved more than 4000 men and women aged 60+years. The individuals had been followed up to 27 years. The incidence of fracture was ascertained during the follow-up period. A unique osteogenomic profile was constructed for each individual from 68 BMD-associated genetic variants. The osteogenomic profile was significantly associated with BMD, fracture risk, and BMD changes. Incorporating the osteogenomic profile into existing prognostic

model improved the prognostic performance over and above of traditional clinical risk factors models (age, gender, prior fracture, and history of fall). The area under the receiver operating characteristic curve for model with the osteogenomic profile was 71.1%, an increase of 0.5% compared with the model without the profile. More importantly, reclassification analysis showed that compared with the clinical risk factor (CRF) model, adding GRS resulted in 16% of individuals moving correctly from one risk category to another. In decision curve analysis, I found that for risk threshold greater than 15%, the osteogenomic profile could help reduce the number of unnecessary treatments. I also demonstrated that the predictive accuracy of fracture prediction using artificial neural network model was improved to 87% (AUC 0.94), which was significantly higher than that for the Cox's proportional hazards model (Accuracy 82%, AUC 0.85) or the Garvan model (Accuracy 83%, AUC 0.86).

In conclusion, this thesis shows that an osteogenomic profile constructed from multiple BMD associated genetic variants is associated with fracture risk, and that the incorporation of osteogenomic profile could enhance the accuracy of fracture risk assessment for an individual men and women.

PUBLICATIONS ARISING FROM THIS THESIS

Published Papers

1. Mai, H. T., Tran, T. S., **Ho-Le, T. P.,** Pham, T. T., Center, J. R., Eisman, J. A., & Nguyen, T. V. (2018). Low-trauma rib fracture in the elderly: Risk factors and mortality consequence. Bone, 116, 295-300. doi:10.1016/j.bone.2018.08.016

2. **Ho-Le, T. P.,** Pham, H. M., Center, J. R., Eisman, J. A., Nguyen, H. T., & Nguyen, T. V. (2018). *Prediction of changes in bone mineral density in the elderly: contribution of "osteogenomic profile"*. Arch Osteoporos, 13(1), 68. doi:10.1007/s11657-018-0480-2

3. Ho-Pham, L. T., **Ho-Le, T. P**., Mai, L. D., Do, T. M., Doan, M. C., & Nguyen, T. V. (2018). *Sex-difference in bone architecture and bone fragility in Vietnamese*. Sci Rep, 8(1), 7707. doi:10.1038/s41598-018-26053-9

4. **Ho-Le, T. P.**, & Nguyen, T. V. (2018). *Mathematics Research in Association of Southeast Asian Nations Countries: A Scientometric Analysis of Patterns and Impacts*. Frontiers in Research Metrics and Analytics, 3(3). doi:10.3389/frma.2018.00003

5. **Ho-Le TP**, Center JR, Eisman JA, Nguyen HT, Nguyen TV. *Prediction of Hip Fracture in Post-menopausal Women using Artificial Neural Network Approach*. 39th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC), 11-15 July 2017; 10.1109/EMBC.2017.8037784

6. Nguyen TV, **Ho-Le TP**, Le UV. *International collaboration in scientific research in Vietnam: an analysis of patterns and impact*. Scientometrics. journal article, Feb 2017;110(2):1035-51.

7. **Ho-Le TP**, Center JR, Eisman JA, Nguyen HT, Nguyen TV. *Prediction of Bone Mineral Density and Fragility Fracture by Genetic Profiling*. Journal of Bone and Mineral Research. Feb 2017;32(2):285-93.

8. Pham HM, Nguyen SC, **Ho-Le TP**, Center JR, Eisman JA, Nguyen TV. *Association of Muscle Weakness With Post-Fracture Mortality in Older Men and Women: A 25-Year Prospective Study*. Journal of bone and mineral research. Nov 2016. Epub 2016/11/20.

Manuscripts Submitted or In Preparation

9. **Ho-Le, T. P**., Thach S. Tran, Jacqueline R. Center, John A. Eisman, Tuan V. Nguyen (2018), *Contribution of Multimorbility to Post-Fracture Mortality : A Latent Class Analysis Approach – In preparation.*

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9. ***Thao P. Ho-Le**, Jacqueline R. Center, John A. Eisman, Hung T. Nguyen, Tuan V. Nguyen (2017). *Determination of risk threshold for osteoporosis therapy: a decision curve analysis approach.* 27th Annual Scientific Meeting of the ANZBMS, Brisbane.

10. ***Ho-Le TP**, Center JR, Eisman JA, Nguyen HT, Nguyen TV (2017). *Accurate Prediction of Hip Fracture by Machine Learning Approach*. 27th Annual Scientific Meeting of the ANZBMS, Brisbane.

11. ***Thao P. Ho-Le**, Jacqueline R. Center, John A. Eisman, Tuan V. Nguyen, Hung T. Nguyen (2017). *Prediction of Hip Fracture in Post-menopausal Women using Artificial Neural Network Approach*. 39th Annual International Conference of the IEEE Engineering in Medicine and Biology Society, Jeju.

12. **Ho-Le TP**, Center JR, Eisman JA, Nguyen HT, Nguyen TV (2017). *Genetic prediction of lifetime risk of fracture*. WCO-IOF-ESCEO conference, Florence.

13. **Thao P. Ho-Le**, Hanh M. Pham, Jacqueline R. Center, John A. Eisman, Hung T. Nguyen, Tuan V. Nguyen (2016). *Genetic Profiling Predicts Bone Loss and Bone Mineral Density*, 38th Annual Scientific Meeting of the American society for Bone and Mineral Research, Atlanta.

14. ***Ho-Le TP**, Center JR, Eisman JA, Nguyen HT, Nguyen TV (2016). *Prediction of bone mineral density and fragility fracture by genetic profiling*, 38th Annual Scientific Meeting of the American society for Bone and Mineral Research, Atlanta.

15. ***Ho-Le TP**, Center JR, Eisman JA, Nguyen HT, Nguyen TV (2016). *Prediction of fracture by genetic profiling*. Vietnamese Osteoporosis conference, Nha Trang, Vietnam.

16. ***Thao P. Ho-Le**, Hanh M. Pham, Jacqueline R. Center, John A. Eisman, Hung T. Nguyen, Tuan V. Nguyen (2016). *Genetic Profiling of 68 SNPs is Associated with Femoral Neck Bone Loss*. Annual Meetings of the Endocrine Society of Australia and Society for Reproductive Biology and Australia and New Zealand Bone and Mineral Society, Gold Coast, Australia.

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ANOVA	analysis of variance
ANN	artificial neural network
AR	absolute risk
AUC	area under the receiver operating characteristic curves
BMC	bone mineral content
BMD	bone mineral density
CI	confidence interval
DNA	deoxyribo-nucleic acid
DOES	Dubbo Osteoporosis Epidemiology Study
DXA	dual X-ray absorptiometry
DZ	dizygotic twins
FNBMD	femoral neck bone mineral density
GWAS	genome-wide association study
HR	hazard ratio
HWE	Hardy Weinberg equilibrium
LD	linkage disequilibrium
LOD	logarithm of the odds
LSBMD	lumbar spine bone mineral density
MAF	minor allele frequency
MZ	monozygotic twins
OR	odds ratio
PAR	population attributable risk
PCR	polymerase chain reaction
QCT	quantitative computed tomography
QUS	quantitative ultrasound
RCT	randomised controlled trial
RNA	ribonucleic acid
ROC	receiver operating characteristic curve
RR	relative risk
SD	standard deviation
SNP	single nucleotide polymorphism