Predicting psychological well-being from genes balance/stoichiometry

(cross-cohort cross-validation)

The concept of psychological well-being refers to a subjective perception of quality of life. Philosophers distinguish between hedonic and eudemonic forms of well-being. In laymen's terms hedonic well-being relates to happiness in life, while eudemonic well-being is achieved by self-realization. In practice, both forms of psychological well-being are highly correlated and can be unified into a single two-class assessment of human mental health: languishing vs. flourishing (Keyes, 2002; Keyes and Simoes, 2012). Interestingly, despite subjective assessment of well-being, a growing body of evidence shows that psychological well-being has a profound effect on human health and longevity (Pressman et al., 2019). For example, several epidemiological longitudinal studies showed that positive well-being associates with reduced risks of all-cause of mortality in both healthy and diseased individuals (Chida and Steptoe, 2008; Petrie et al., 2018; Steptoe and Wardle, 2011; Tamosiunas et al., 2019). Although the relation between the well-being and the risks of mortality remains a debatable issue (de Souto Barreto and Rolland, 2016; Kubzansky et al., 2016; Liu et al., 2016; Stringer and Veldkamp, 2016), a prevailing consensus is that happy people may leave longer (Boehm and Kubzansky, 2012; Diener and Chan, 2011). This idea is also supported by a direct experimental evaluation of an impact of positive well-being on resistance to illness. For example, two studies on 460 volunteers demonstrated that people with positive emotional style exhibited greater resistance to common cold viruses (influenza and rhinovirus) (Cohen et al., 2003; Doyle et al., 2006). This, in turn, indicates well-being as a predictive factor for human health.

Motivated by this reasoning we were wondering if it is possible to predict psychological well-being, i.e. languishing and flourishing, from the balance (stoichiometry) in gene expression networks. To this end, we used peripheral blood mononuclear cells (PBMC) transcriptomic profiles from two studies of adult volunteers from the Durham and Orange County regions of North Carolina as the discovery cohort (training). This cohort included 253 individuals (60% women) of age ~48 ± 8 (Fredrickson et al., 2015; Fredrickson et al., 2013). The validation cohort included 98 male Japanese IT workers of age 48 ± 5 (Kitayama et al., 2016). All individuals were categorized as being languished or flourished based on hedonic and eudemonic well-being scores. The predictive model was trained with XGBoost algorithm using gene stoichiometries feature space. The results shown in Figure 1 clearly indicate that

well-being can be predicted from gene stoichiometry signatures and generalized between distinct cohorts.

As already stated, subjective assessment of psychological well-being may serve as a proxy to mental and physical health. In turn, our results demonstrate that well-being could be potentially an objective body-mind state determined by balance in gene expression networks. As such, we propose that objective monitoring of individual's flourishing based on our predictive model could provide a valuable diagnostic tool. For example, this could be used to monitor mental-physical health of elderly people or of patients following rehabilitation from certain illnesses.

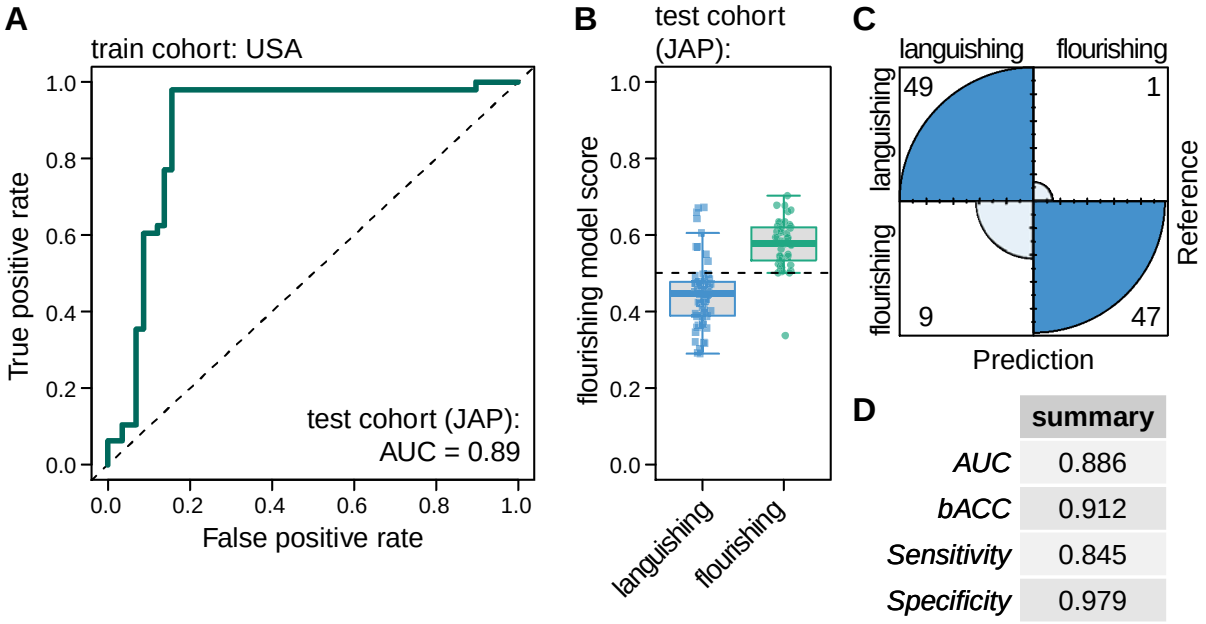

Figure 1. Summary of well-being predictive model. Model was trained on USA cohort (Fredrickson et al., 2015; Fredrickson et al., 2013) and validated for male Japanese IT workers (JAP) (Kitayama et al., 2016). **A)** ROC curve for the test cohort. **B)** Boxplots of flourishing model score for the test cohort. Dashed line indicates classification cut-off estimated by minimization of a distance between ROC curve and (0,1) point. **C)** 2X2 confusion matrix plot for the test cohort. **D)** Model summary for the test cohort. bACC – balanced accuracy (bACC = (Sensitivity + Specificity)/2).

Boehm, J.K., and Kubzansky, L.D. (2012). The heart's content: the association between positive psychological well-being and cardiovascular health. Psychological bulletin *138*, 655-691.
Chida, Y., and Steptoe, A. (2008). Positive psychological well-being and mortality: a quantitative review of prospective observational studies. Psychosomatic medicine *70*, 741-756.
Cohen, S., Doyle, W.J., Turner, R.B., Alper, C.M., and Skoner, D.P. (2003). Emotional style and susceptibility to the common cold. Psychosomatic medicine *65*, 652-657.
de Souto Barreto, P., and Rolland, Y. (2016). Happiness and unhappiness have no direct effect on mortality. Lancet *387*, 822-823.
Diener, E., and Chan, M.Y. (2011). Happy People Live Longer: Subjective Well-Being Contributes to Health and Longevity. Applied Psychology: Health and Well-Being *3*, 1-43.
Doyle, W.J., Gentile, D.A., and Cohen, S. (2006). Emotional style, nasal cytokines, and illness expression after experimental rhinovirus exposure. Brain, behavior, and immunity *20*, 175-181.
Fredrickson, B.L., Grewen, K.M., Algoe, S.B., Firestine, A.M., Arevalo, J.M., Ma, J., and Cole, S.W. (2015). Psychological well-being and the human conserved transcriptional response to adversity. PloS one *10*, e0121839.
Fredrickson, B.L., Grewen, K.M., Coffey, K.A., Algoe, S.B., Firestine, A.M., Arevalo, J.M., Ma, J., and Cole, S.W. (2013). A functional genomic perspective on human well-being. Proceedings of the National Academy of Sciences of the United States of America *110*, 13684-13689.
Keyes, C.L. (2002). The mental health continuum: from languishing to flourishing in life. Journal of health and social behavior *43*, 207-222.
Keyes, C.L., and Simoes, E.J. (2012). To flourish or not: positive mental health and all-cause mortality. American journal of public health *102*, 2164-2172.
Kitayama, S., Akutsu, S., Uchida, Y., and Cole, S.W. (2016). Work, meaning, and gene regulation: Findings from a Japanese information technology firm. Psychoneuroendocrinology *72*, 175-181.
Kubzansky, L.D., Kim, E.S., Salinas, J., Huffman, J.C., and Kawachi, I. (2016). Happiness, health, and mortality. Lancet *388*, 27.
Liu, B., Floud, S., Pirie, K., Green, J., Peto, R., Beral, V., and Million Women Study, C. (2016). Does happiness itself directly affect mortality? The prospective UK Million Women Study. Lancet *387*, 874-881.
Petrie, K.J., Pressman, S.D., Pennebaker, J.W., Overland, S., Tell, G.S., and Sivertsen, B. (2018). Which Aspects of Positive Affect Are Related to Mortality? Results From a General Population Longitudinal Study. Annals of behavioral medicine : a publication of the Society of Behavioral Medicine *52*, 571-581.
Pressman, S.D., Jenkins, B.N., and Moskowitz, J.T. (2019). Positive Affect and Health: What Do We Know and Where Next Should We Go? Annual review of psychology *70*, 627-650.
Steptoe, A., and Wardle, J. (2011). Positive affect measured using ecological momentary assessment and survival in older men and women. Proceedings of the National Academy of Sciences of the United States of America *108*, 18244-18248.
Stringer, S., and Veldkamp, C.L. (2016). Happiness, health, and mortality. Lancet *388*, 26.
Tamosiunas, A., Sapranaviciute-Zabazlajeva, L., Luksiene, D., Virviciute, D., and Peasey, A. (2019). Psychological well-being and mortality: longitudinal findings from Lithuanian middle-aged and older adults study. Social psychiatry and psychiatric epidemiology.