A Prevention Strategy for the Indication of Prune Consumption in Perimenopausal Women

Principal Investigator: Mary Jane De Souza, PhD, Distinguished Professor of Kinesiology and Physiology, Penn State University
Co-Investigator: Nancy I Williams, ScD, Professor of Kinesiology and Physiology, Penn State University
Co-Investigator: Connie J. Rogers, PhD, MPH. Professor of Nutritional Science, University of Georgia
Menopause Consultant: Nanette Santoro, MD. Professor and E Stewart Taylor Chair of Obstetrics & Gynecology, University of Colorado School of Medicine
Biostatistician: Hang Lee, PhD. Professor of Biostatistics. Harvard Medical School.

According to a survey on healthcare in the United States, women are highly engaged in their health decisions and pursue knowledge to empower their healthcare decision-making aggressively, especially as they approach menopause. In the survey, women expressed an eagerness to embrace and utilize wellness-oriented healthcare strategies and wanted innovative holistically focused healthcare options that allow for greater accountability and responsibility. In fact, women represent a consumer demographic that wants more progressive decision-making power over their healthcare decisions, especially during the years before menopause starts called the perimenopausal years.

The perimenopausal demographic of women represents an opportunistic group of women that the CPB could target to message the benefits of prunes that were observed in postmenopausal women. Funding a project to test the benefits of prunes on preserving bone in this high-risk group is valuable because it is during the last year of perimenopause, called transmenopause, that the most bone is lost in women- approximately 6-7% in that single year alone! As such, a prevention project targeting women in the transmenopause or the late perimenopausal window is of great value to prune stakeholders and represents a new and important demographic to target as they are a group with substantial purchasing power. A positive study in this demographic could be transformative, provide a prevention indication where there is none in the field, and significantly advance the CPB goals described in the Nutrition Research RoadMap. On pages 30-31 in the CPB Roadmap, it is stated that a primary goal is "*to conduct clinical bone health studies in unexplored life stages*". Perimenopause is a life stage yet to be explored by the CPB, and prevention rather than treatment would be transformative for perimenopausal women and in turn for the CPB to attract a new demographic.

Menopause is officially defined as the last menstrual cycle in a woman's life and marks the end of her reproductive years. Perimenopause is the time of transition between a woman's reproductive years and menopause. Menopause, the permanent cessation of menses and ovarian function, is associated with very low levels of estrogen, heightened inflammation, and accelerated bone loss.   Menopause is preceded by a transition state referred to as the perimenopause and is best described by the gradual loss of estrogen, menses fluctuations, and irregular menstrual patterns. This time period is also associated with the initiation of accelerated bone loss, especially during the late perimenopausal phase.

The approximate three-year transition from perimenopause to postmenopause is a significant time of rapid bone loss in women, with average declines in hip bone mineral density (BMD) of 6% and lumbar spine BMD of 7% during the last year before the final menstrual period. This last year before the final menstrual period is defined as the transmenopausal transition time period and encompasses the late perimenopausal time period. It is most noteworthy that the first year prior to the final menstrual period is the year of **the** most significant volume of bone loss during the entire peri and postmenopausal period. In fact, postmenopausal bone loss rates are <u>less</u> than the bone loss rates observed during the transmenopausal and late perimenopausal time periods. Moreover, the decline in BMD that is observed occurs in concert with deleterious changes in bone structure, considered to be one of the most significant threats of increasing risk of fracture during this transition.

A most exciting fact for the CPB to consider is that targeting the late perimenopausal time period for women is when 1) they are most interested in seizing opportunities to proactively manage their health, and 2) it is a time period during which prunes can be used as a prevention paradigm, rather than a treatment paradigm. This approach presents a unique opportunity to target a new population for CPB industry stakeholders to test whether prunes, already demonstrated to maintain BMD in postmenopausal women, can be used to prevent the rapid decline of bone loss during the transmenopausal or late perimenopausal time periods. Another intriguing factor to consider is that the transmenopausal or late perimenopausal time periods are a time where

drug therapy in the clinical world of medicine is never initiated PRIOR to bone loss, even if that bone loss is anticipated to be rapid and significant. This fact makes a prevention indication extremely attractive for this vulnerable group of women during perimenopause for the CPB. Moreover, and similar to the PSU Prune Study in postmenopausal women, we can create a rich biobank of samples during the execution of the RCT we complete in this population to stretch the body of work and maximize the outcomes from such a study.

With the ability to clearly identify the transmenopause time period as a result of the wonderful work published by the Study on Women's Health Across the Nation (The Swan Study), and the ReSTAGE Studies of mid-life women, we are now well equipped to study the transmenopause or late perimenopausal time periods for the CPB. We project that a study that focuses on women in this age range (47-54) would provide immeasurable benefits for the translation of results to the community of women impacted, and in turn, provide an entirely new demographic of interest to the prune industry, and an entirely new indication- that of prevention (rather than treatment).

As defined by the ReSTAGE Study investigators, we too shall define the late perimenopausal time period as that time period when a woman had had no menses for the past 60 days, coupled with some irregular bleeding in the past 11 months. The utilization of a marker of ovarian reserve, serum anti-Mullerian hormone (AMH) concentration, can help to confirm the late perimenopause time period with great accuracy and with a sensitivity of 80%. As such, and as previously stated, there is firm confirmation in the literature that there is a period of rapid BMD loss that actually brackets the final menstrual period, commencing one year prior and continuing two years beyond the final menstrual period, i.e., the transmenopausal time period. Previously, the identification of the different phases of perimenopause has hampered studies targeting the prevention of bone loss due to the difficulty encountered in isolating this period. With the advancement of 30 years of data studying the bleeding patterns in the SWAN and ReSTAGE cohorts and the development of assays to detect AMH, much progress has been made in recent years. The timing of the late perimenopausal time period and the final menstrual period can be consistently and reliably predicted within a window of 12-18 months by the use of menstrual bleeding patterning and a high-sensitivity test of serum AMH concentration We shall use menstrual bleeding patterns, as defined by ReSTAGE investigators, and the predictive values of serum AMH patterning to reliably predict the late perimenopausal and transmenopausal time period for the proposed study.

In summary, the strategy proposed represents a prevention option (in lieu of a treatment option) for a large population of women with purchasing power who have been established to be keenly interested in optimizing their health. As such, the purpose of this proposed research will be to test whether prunes are effective in attenuating the rapid transmenopausal bone loss observed in perimenopausal women during this consequential time period. If successful, the prune industry will be provided a powerful strategy for perimenopausal women to prevent the rapid decline in BMD and decrements in bone strength- in addition to the already established treatment indication proven effective for postmenopausal women.

This is a large project with a budget that is commensurate for such a project. If all components described are completed as described herein, the project could be executed in segments to make it affordable for the California Prune Board to fund. Segment 1 would be funded to complete the main project components to collect all of the DXA and pQCT outcomes, to process all samples for the determination of the number of circulating activated monocytes and LPS-stimulated PBMC supernatants for cytokines and to collect all serum, and fecal samples to create a large biobank for the study. Segment 2 would be budgeted to fund all of the serum and fecal analyses of bone signaling and inflammation pathways, gut permeability and gut microbiome analyses, the cost of publications, and the cost of travel for presentations of the data at conferences. Further creative funding options are possible upon request. The estimated cost for this project is 900K-1.3K, very similar to the cost of the PSU postmenopausal Prune Study.

Nutrition Research Program Budget Review

Study ($K)	FY23/24	FY24/25	FY25/26	FY26/27
Trans/perimenopause/NIFA	--	$750	--	--
Japan Research Advisement	$20	--	--	--
Prebiotic/Biobank/De Souza	$168	$168	--	--
Calcium Utilization Study/Cao	$100	$125	--	--
Mitigate Hormonal Contraceptives/ Hooshmand & Kern	$73	--	--	--
Manuscripts & Presentations/De Souza	$37	--	--	--
Manuscript: Colon Cancer Protection/Turner	$13	--	--	--
Food Survey Audit/Lemay	$7	--	--	--
Fecal Transplant/McCabe	--	$48	--	--
Prevention of Glucocorticoid Induced Osteoporosis/ McCabe	--	$25	--	--
Sample Packs/Other	$25	$20	$20	$20
Total Expenditures	$443	$1,136	$20	$20
Budget Guidance for Committee Planning	$400	$808	$400	$400
Rollover Budget from Previous Year	$371	$328		
Unspent Budget	$328	$0	$380	$380

Covered by rolling 3 year "Agreement in Principle"