Brief literature review of some publications where IBEX C2C-HUSA ELISA assay was used.

- A population-based cohort with pre-radiographic disease and radiographic OA was evaluated at baseline and follow-up after 3.3 years. The study revealed that IB-C2C-HUSA degradation assay detects the generation of a pathology-related cartilage collagen peptide(s) that progressively increase(s) with onset of knee articular cartilage degeneration. Cross-sectionally, the assay could discriminate between the subgroups with the highest level of C2C-HUSA biomarker seen in radiographic OA group (Figure A). There was a progressive increase in C2C-HUSA levels with increasing cartilage degradation.

- Moreover, in subject already exhibiting cartilage pathology, analysis of baseline urine with C2C-HUSA assay was predictive of subsequent cartilage loss over 3 years, with progressors showing significantly increased levels compared to non-progressors (Figure B). (Poole et al. 2016).

- In an OA initiative head to head assessment of 18 biomarkers, C2C-HUSA was one of 8 biomarkers that predicted case status and one of only 2 biomarkers, the other one being CTX-II, that predicted individual group status, including pain worsening, joint space loss and their combination (Kraus et al. 2016).

- Tamm et al. (2014) also observed positive correlations with symptoms as well as joint function in a study with middle age patients with knee OA.

- In a recent study of adolescent and adult volleyball athletes, uC2C levels were reduced in adolescent with closed growth plates compared to open growth plates. In adults, uC2C as well as uCTX-II levels, showed a marked reduction from adolescent levels. Greater levels of uC2C in adolescents than in adults may reflect increased cartilage turnover in response to higher joint loading. (Boeth et al. 2017).

