Biochemical Markers in OA

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Time to knee replacement

enrollment enriched for progressors

early evidence of treatment effect

Clinically Relevant Progression (radiographic AND pain)

PRIMARY NEED for DRUG DEVELOPMENT in OA: PROGNOSTIC BIOCHEMICAL MARKERS LINKED TO <u>CLINICALLY RELEVANT OUTCOMES</u>

accelerated drug approval

early disease treatment

Development of incident radiographic OA

CURRENT EVIDENCE

Single baseline measures in LONGITUDINAL TRIALS

urinary CTXII

serum/plasma CRTAC1

QUALIFICATION EFFORTS

urinary CTXII

enrollment enriched for progressors

early evidence of treatment effect

‘selection biomarkers’ for enrolling patients into clinical studies increase the likelihood of drug approval (from 8% to 26%)

accelerated drug approval

early disease treatment

DISCLOSURE: Patent pending related to proteomic panel for OA

Thomas et al. Clinical Development Success Rates 2006-2015 - BIO, Biomedtracker, Amplion 2016.pdf

‘Suspension Bridging’ Concept

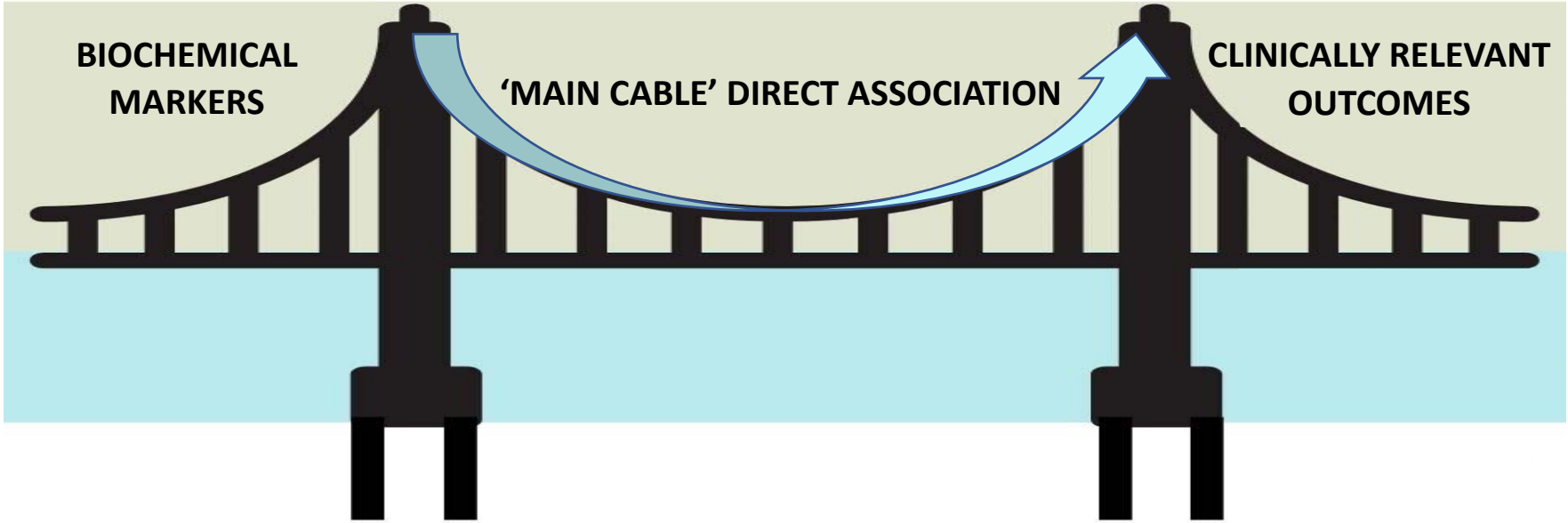
urinary C-terminal telopeptide of type II collagen

Serum/plasma Cartilage acidic protein 1 precursor

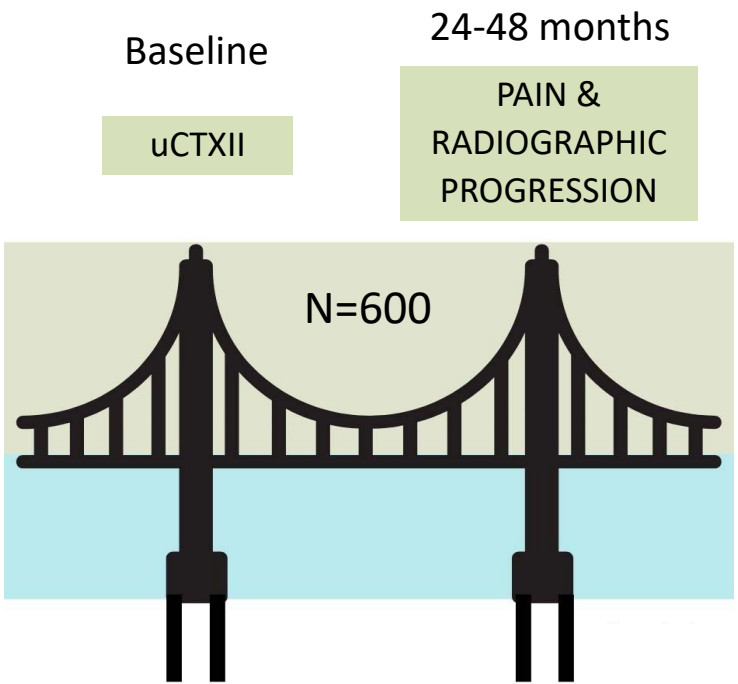
uCTXII
s/pCRTAC1 (CRAC1)

clinically relevant outcomes

Clinically Relevant Progression
(worsening Pain AND Radiograph)
Total Joint Replacement



Predicts Clinically Relevant Knee OA Progression - uCTXII



- uCTXII predicted clinically relevant knee OA progression: odds ratio (OR) 1.29
- **AUC 0.608**

FNIH Biomarker Consortium for OA
Kraus et al. 2017 PMID 27296323
(AUC unpublished)

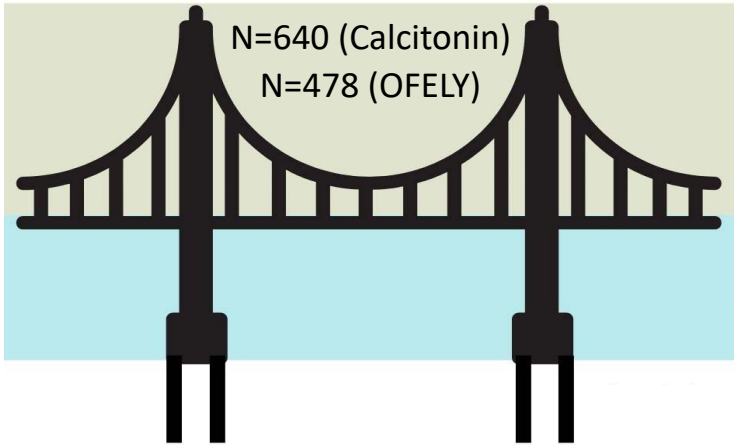
Predicts Total Joint (KNEE/HIP) Replacement – uCTXII

Baseline

uCTXII

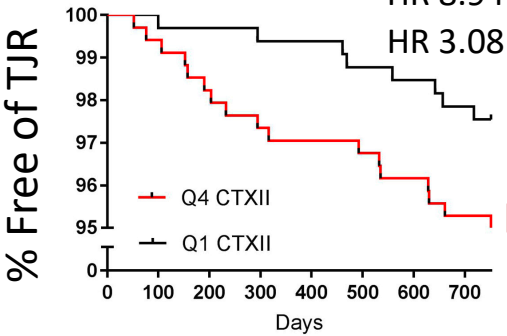
2 years (Calcitonin)
18 years (OFELY)

TJR



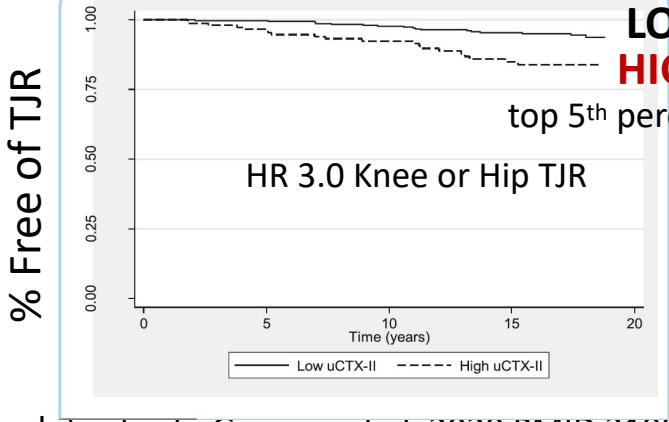
CALCITONIN

HR 8.94 Knee TJR
HR 3.08 Knee or Hip TJR



Calcitonin Trials; Bjerre-Bastos et al. 2019 OARSI S31:12

OFELY

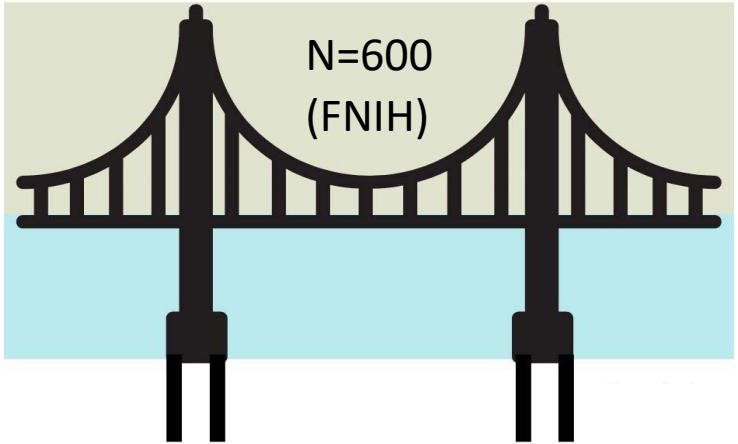


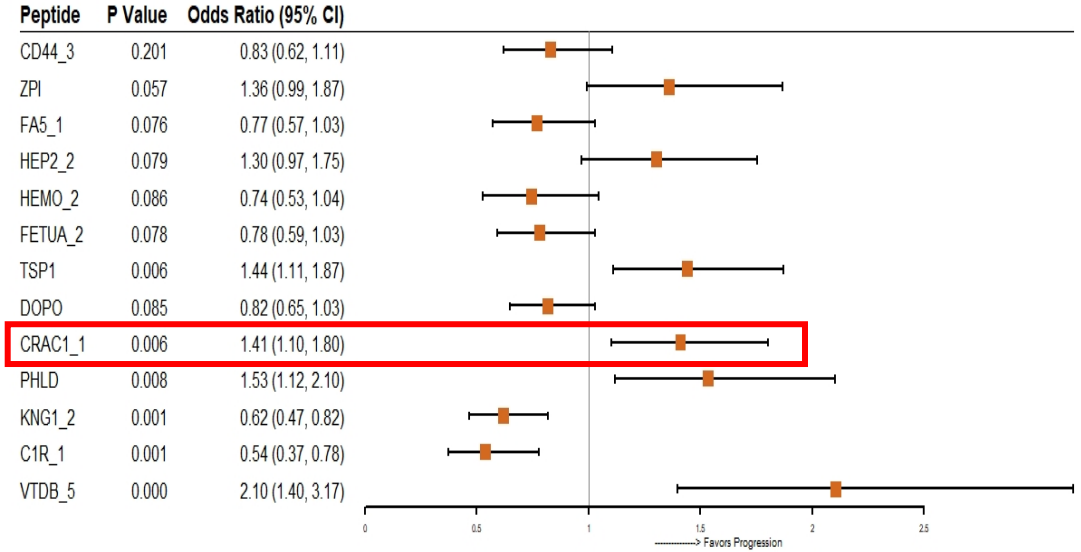
OFELY (female) cohort ; Garnero et al. 2020 PMID 31982562

Predicts Clinically Relevant Knee OA Progression – sCRTAC1

Pain & JSL Progression (13 peptides): AUC=0.740

Baseline	24-48 months
13 SERUM PEPTIDES BY MASS SPECTROMETRY	PAIN & RADIOGRAPHIC PROGRESSION





JSL Progression AUC=0.698
Validation cohort AUC=0.697
Pain Progression AUC=0.673

Zhou and Kraus et al. 2021 OARSI poster 748

Predicts Total Joint (KNEE/HIP) Replacement – pCRTAC1

- Screened 4,792 SomaScan plasma proteins
- 45 associated with OA--CRTAC1 most highly associated
- CRTAC1 associated with joint pain
- CRTAC1 dropped after surgery (Total Joint Replacement)

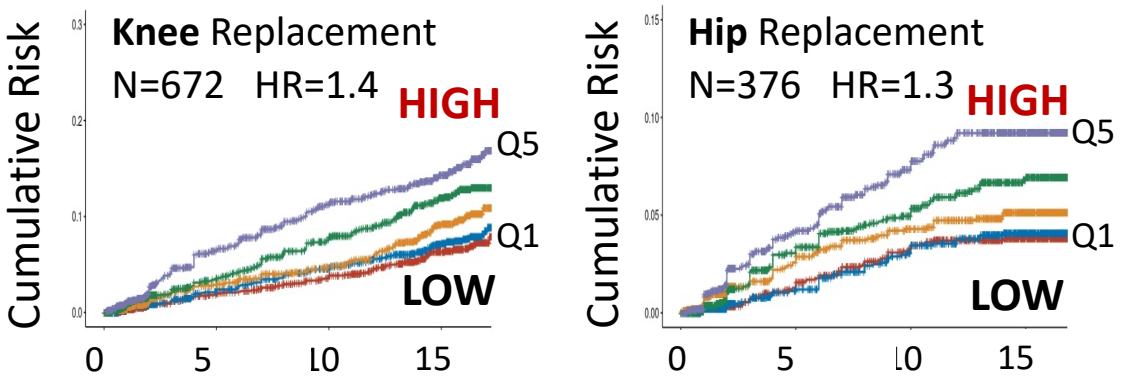
Baseline

pCRTAC1

15 years

Risk of
Total Joint Replacement

CUMULATIVE RISK OF JOINT REPLACEMENT BASED ON CRTAC1 ALONE

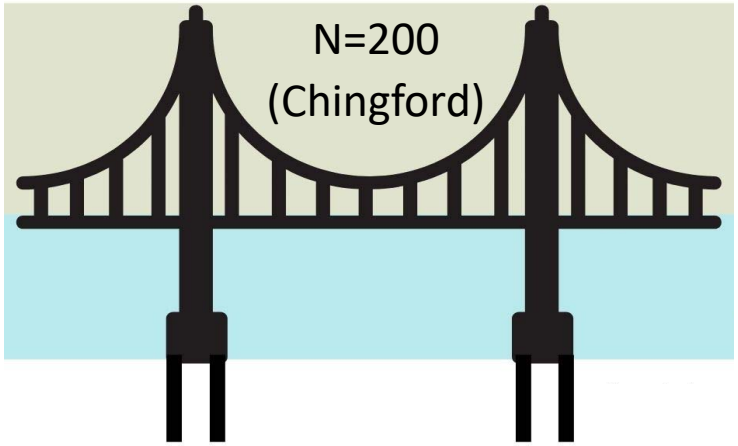


Time from plasma collection (years)

Styrkarsdottir et al. Arthritis Rheum 2021 PMID:33982893

Predicts Incident Radiographic Knee OA – sCRTAC1

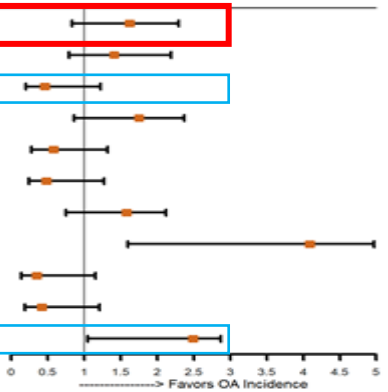
Baseline	4-8 years
6-11 SERUM PEPTIDES BY MASS SPECTROMETRY	INCIDENT RADIOGRAPHIC KNEE OA



8 YEARS AHEAD AUC 0.76

Variable	P Value	Odds Ratio (95% CI)
CRAC1_1	0.16	1.62(0.83,2.29)
APOE	0.25	1.41(0.79,2.19)
PRG4_1	0.067	0.46(0.2,1.22)
HPT_1	0.12	1.75(0.86,2.37)
CO5_5	0.148	0.58(0.28,1.32)
LYAM1	0.038	0.48(0.24,1.27)
COMP_1	0.227	1.58(0.75,2.12)
HABP2_2	0.003	4.09(1.6,4.97)
VTNC	0.028	0.35(0.14,1.15)
FBLN1	0.028	0.42(0.19,1.21)
HRG_4	0.038	2.49(1.05,2.87)

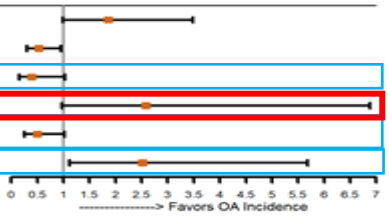
Model AUC(95% CI): 0.76 (0.70,0.82)



4 YEARS AHEAD AUC 0.77

Variable	P Value	Odds Ratio (95% CI)
COMP_1	0.052	1.86(0.99,3.48)
FBLN3_2	0.036	0.53(0.3,0.95)
PLF4	0.056	0.39(0.15,1.03)
CRAC1_1	0.056	2.58(0.97,6.88)
RET4	0.057	0.5(0.25,1.02)
ZPI	0.03	2.52(1.12,5.68)

Model AUC(95% CI): 0.77 (0.67,0.86)



Sun and Kraus et al. 2021 OARSI poster 741

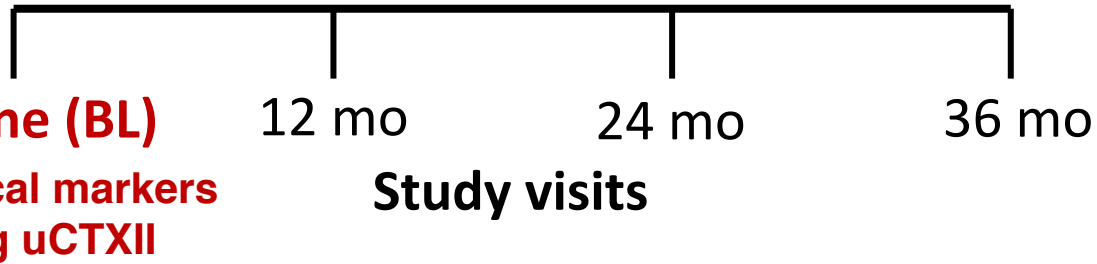
Clinical Evaluation and Qualification by FDA of Osteoarthritis Biomarkers
FNIH Biomarkers Consortium

https://fnih.org/our-programs/biomarkers-consortium/programs/progress-oa

Biochemical Biomarkers: measured at baseline in ***placebo*** arms of 2 clinical trials—(n=871)

MRI Biomarkers: measured at baseline in ***placebo*** arms of *5* clinical trials—(n=434)

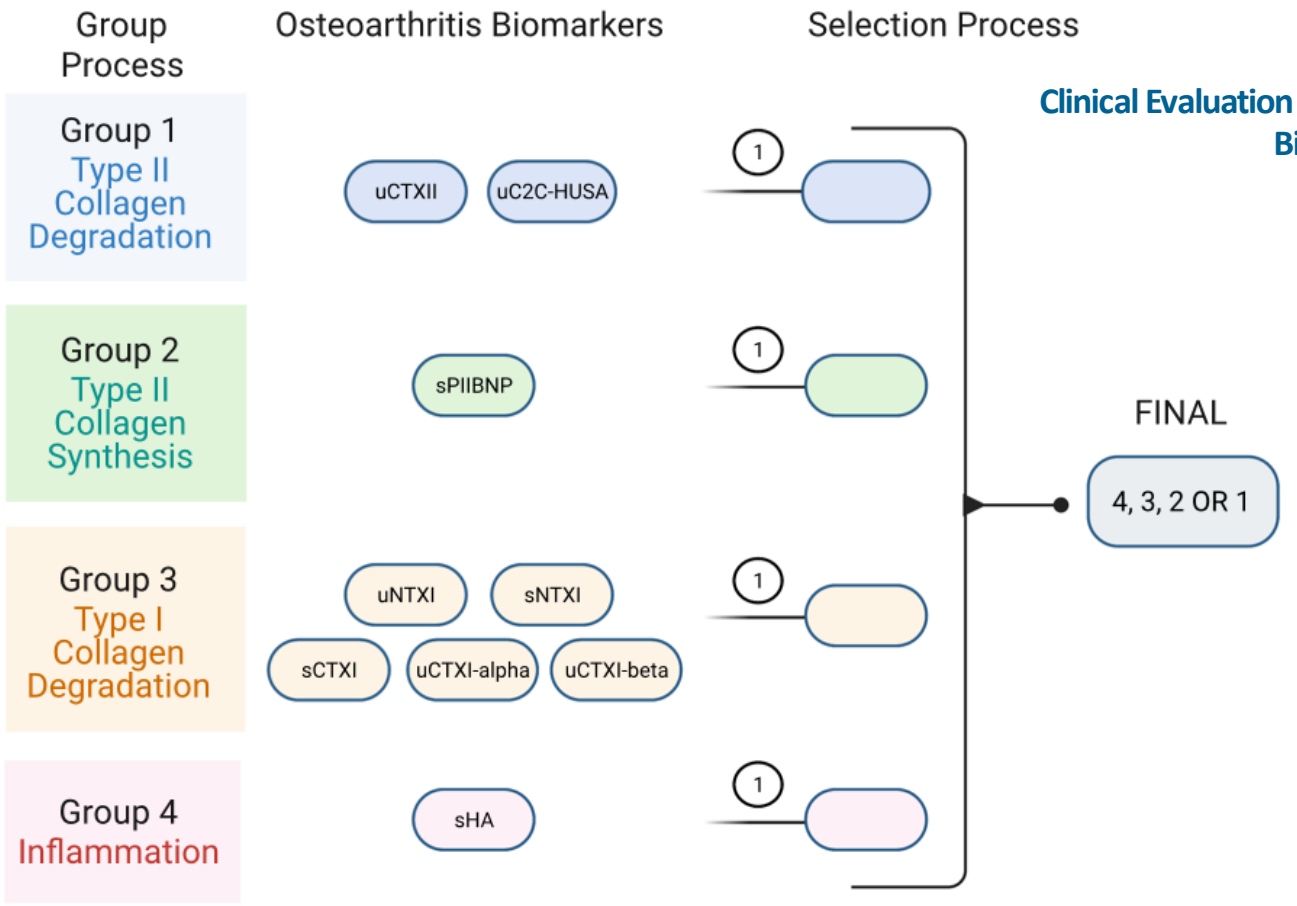
Trabecular Bone Texture (radiographic) Biomarkers: measured at baseline in ***placebo*** arms of 6 clinical trials (n=1271)



- **Endpoint:** 24M (12M when 24M unavailable; 36M ancillary when available)
- **Primary Outcome:** Radiographic progression (0.7 mm joint space narrowing)
- **Secondary Outcomes:** Radiographic (0.5 mm joint space narrowing); Pain; Radiographic+Pain Progression

BIOMARKERS CONSORTIUM FNIH

Clinical Evaluation and Qualification of 9 Osteoarthritis Biochemical Biomarkers



Notes: s=serum, u=urine, urine biomarkers are normalized to Creatinine

BIOMARKERS CONSORTIUM FNIH

FNIH PROGRESS OA Project – Regulatory Update

FDA Biomarker Qualification Program

21st Century Cures Act

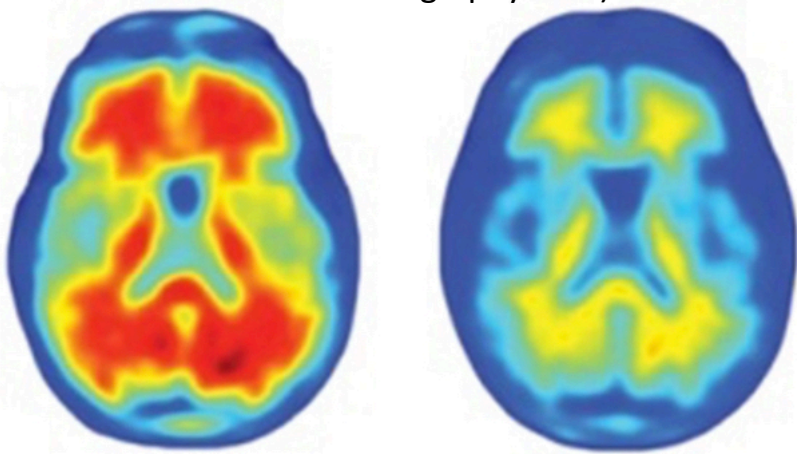
BMQ Step	MRI	Biochemical	TBT
1. LOI	Submitted to FDA 2015; received acceptance	Submitted to FDA 9/2019; Status: LOI accepted 2/2020	Submitted to FDA 9/2019; Status: LOI accepted 2/2020
2. LBQSU	Submitted 11/2018; FDA 507 acceptance letter to move forward 5/2019		
3. QP	Submitted 1/2020; FDA review pending	Submission in preparation	Submission in preparation
4. FQP			

LOI=letter of intent
LBQSU=legacy biomarker qualification status update
QP=qualification plan
FQP=full qualification package

BIOMARKERS CONSORTIUM FNIH

Accelerated Approval – Within Reach for OA?

aducanumab FDA approved for Alzheimer's Disease based on clearing plaques and preventing formation of new plaques of beta amyloid (shown in a positron emission tomography scan)



SEVIGNY *ET AL.*, *NATURE*, 537, 50 (2016)

Phase 4 post-approval trial with clinical patient benefit required

- **Alzheimer's Disease has multiple similarities with OA**
- **Serious disease of unmet need**
- **No treatments on the market "attack the cause of disease rather than just easing symptoms"**
- **High prevalence – patients matter**
  - **Alzheimer's Disease 5.8 million in US**
  - **OA 32.5 million in US**
- **A history of multiple drug failures**
- **Biomarkers now exist in OA that are "<u>reasonably likely to predict important benefits to patients</u>"**
- **OARSI proposed study designs for accelerated approval trials in OA (Kraus et al. 2019 PMID:30465809)**
- **"History has shown us that approvals of the first drug in a new category invigorates the field" (Maria Carrillo, CSO Alzheimer's Association)**

Summary by Kelly Servick Jun. 7, 2021:

https://www.sciencemag.org/news/2021/06/alzheimer-s-drug-approved-despite-doubts-about-effectiveness

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Conclusions

Biochemical markers have been linked to clinically relevant outcomes in OA but more work is needed to establish amount of biomarker change that equates to a clinically meaningful benefit

Demonstration of biomarker relationship to a causal pathway in human OA awaits existence of a disease modifying drug (DMOAD)

Formal qualification of uCTXII as an OA drug development tool is ongoing

CRTAC1 represents a second generation (emerging) biomarker for OA that may be a superior prognostic compared to existing biomarkers

Incident and progressive knee OA share biomarkers and therefore molecular pathophysiology—suggesting the false dichotomy of the radiograph to define "OA" vs no "OA"

Biomarkers that are "reasonably likely to predict important benefits to patients" can be used as endpoints for accelerated drug approval in serious diseases—such as osteoarthritis--with a post-marketing trial to show drug impact on patient relevant outcomes