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Clinical Definitions of Early OA: Implications for Prevention

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The Queen's Anniversary Prizes
For Higher and Further Education
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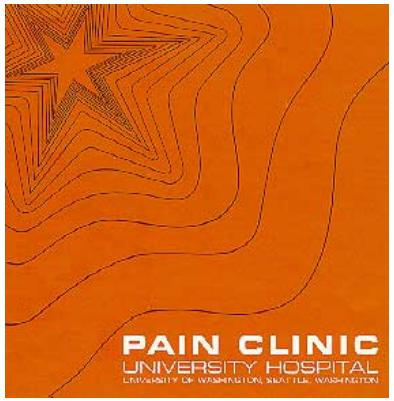

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Outline

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- Conceptual framework, with a personal emphasis
- Findings from existing epidemiologic studies
- New patient-reported measurement of clinical states in early OA
- Timing of emergent symptoms
- A role for the routine electronic health record
- Concluding remarks

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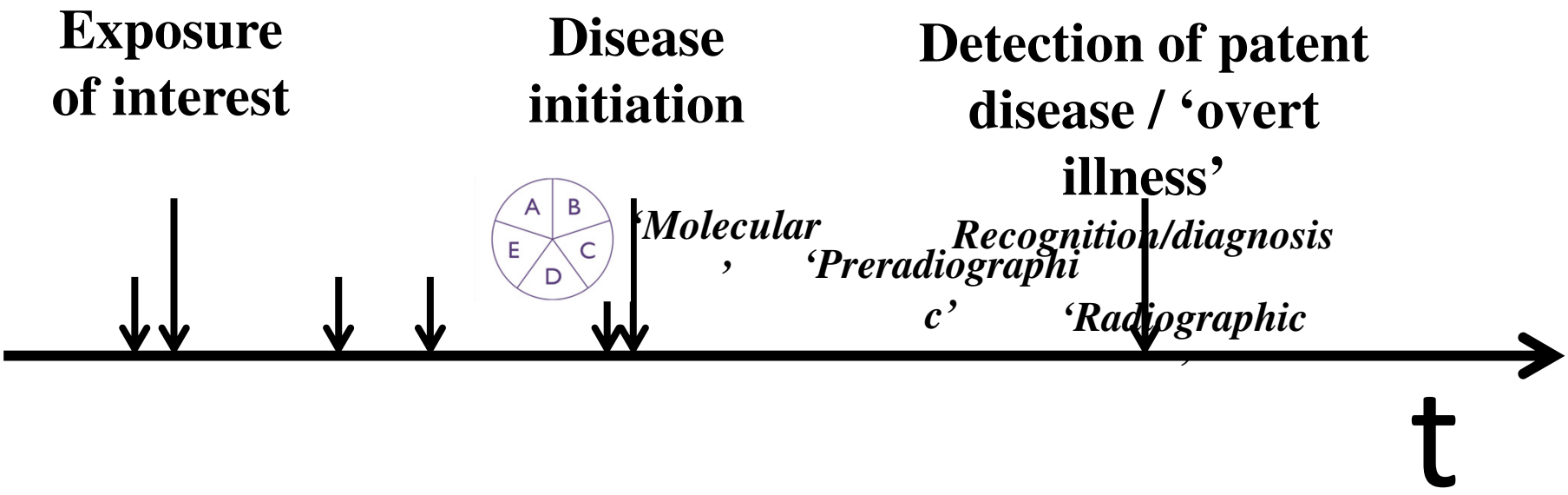
PRIMARY PREVENTION

SECONDARY PREVENTION

TERTIARY PREVENTION



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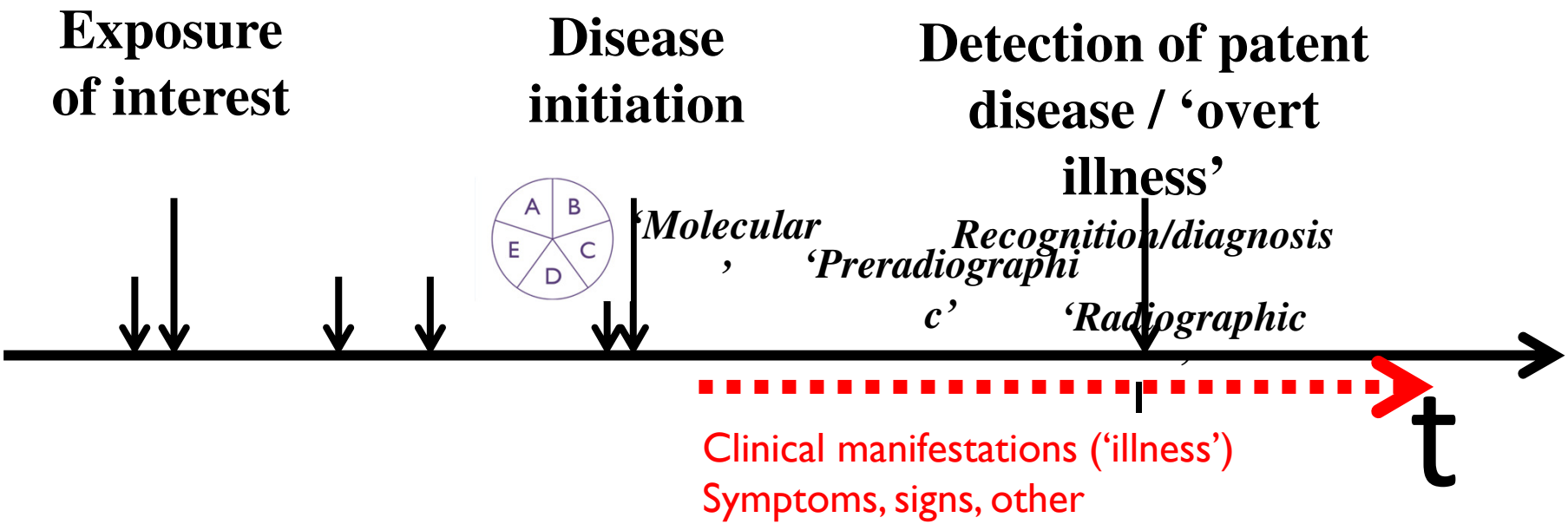
PRIMARY PREVENTION

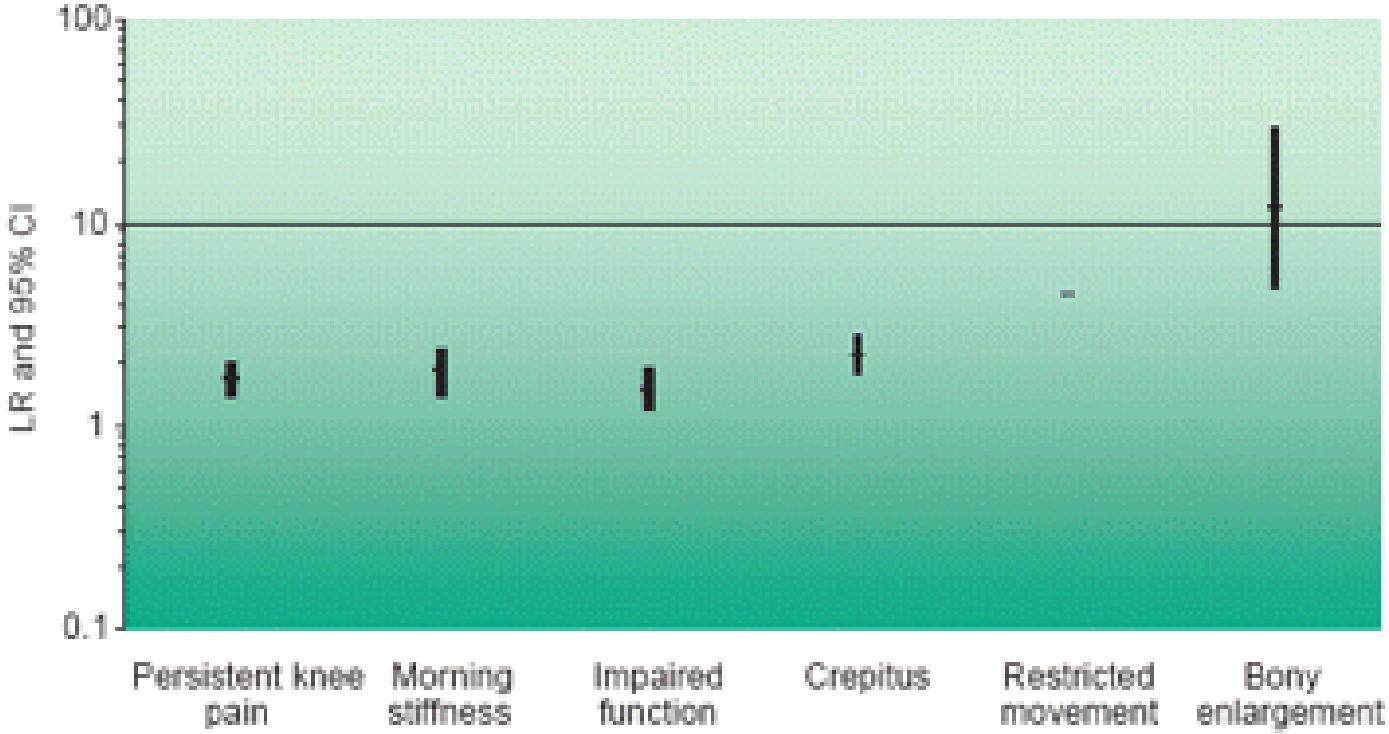
SECONDARY PREVENTION

TERTIARY PREVENTION



Established clinical signs and symptoms

- 2010: Review of literature (313 studies)



Zhang et al (2010)

Cross-sectional association with pre-radiographic anatomical change

RS-III. Open population, 1689 knees, all F, mean age 55 yrs, KL0-1. Outcome: $TFOA_{MRI}$ (ref: No $TFOA_{MRI}$)

	Adj OR (95%CI)
Current knee pain	2.8 (1.8, 4.4)
Knee pain in past year	2.5 (1.7, 3.6)
Knee pain on most days in past month	4.1 (2.4, 7.0)

Schiphof et al. (2014)

Cross-sectional association with pre-radiographic anatomical change

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MoDEKO. Symptomatic, n=255, ~50% F, age 40-79 yrs

	'No OA'† *(n=33)*	'Pre-ROA'‡ *(n=124)*	Adj OR (95%CI)
Abnormal gait %	0	5	3.5 (0.4, >100)
Effusion %	0	16	13.1 (1.7, >100)
Flexion contracture °	0	1	1.7 (1.1, 2.9)
Bony swelling %	27	27	0.9 (0.4, 2.2)

† 'No OA' = MRI cartilage score < 2 and KL < 2
‡ 'Pre-ROA' = MRI cartilage score ≥ 2 & KL < 2

Cibere et al. (2010)

Longitudinal associations with incident ROA

Study	Sample	Baseline predictor	Outcome	OR (95%CI)
Chingford, UK	General pop, mean age 54, n=644-715	Knee pain lasting > 1month	OP at 4 yrs JSN at 4 yrs	1.9 (1.2, 3.1))‡ 0.8 (0.4, 1.4))‡
Bristol, UK	General pop, aged 55+, n=354	Knee on most days for ≥ 1 month in past year	KL≥1 at 5.1 yrs KL≥2 at 5.1 yrs	2.9 (1.2, 6.7)† 1.3 (0.6, 2.7)†
Miyagawa, Japan	General pop, aged 65+, n=261	Knee pain on most days for a month in past year (one or both knees)	KL2+ in both knees at 4 yrs	1.4 (0.9, 2.3)‡
ROAD, Japan	General pop, aged ?23-97, n=1098	Knee pain on most days in addition to now	KL≥2 at 3.3 yrs	0.9 (0.3, 2.2)‡
PROOF, NL	High risk, aged 50-60, n=407	Mild symptoms	Combined ACR, KL≥2, JSN≥1 at 2.5 yrs	1.8 (1.2, 2.7)‡
RS-I, NL	Symp general pop, aged 55+, n=944	General joint complaints in last month	KL≥2 / TKR at 6.1 - 11.5 yrs	2.2 (1.1, 4.4)†

† adjusted OR: *Cooper et al. (2000); De Klerk et al. (2012).* ‡ crude OR: *Hart et al. (1999); Nishimura et al. (2011); Muraki et al. (2012); unpublished data from Runhaar et al. (2015)*

Interpretation

- Conventional clinical signs and symptoms associated with MRI abnormalities and with future incident ROA are found in a proportion of the at-risk population in pre-radiographic stages

Individual risk prediction

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CAS-K: 122 symptomatic, 50+ yrs, KL=0-1

Outcome: Incident KL≥ 2 (TF and PF) at 3 years

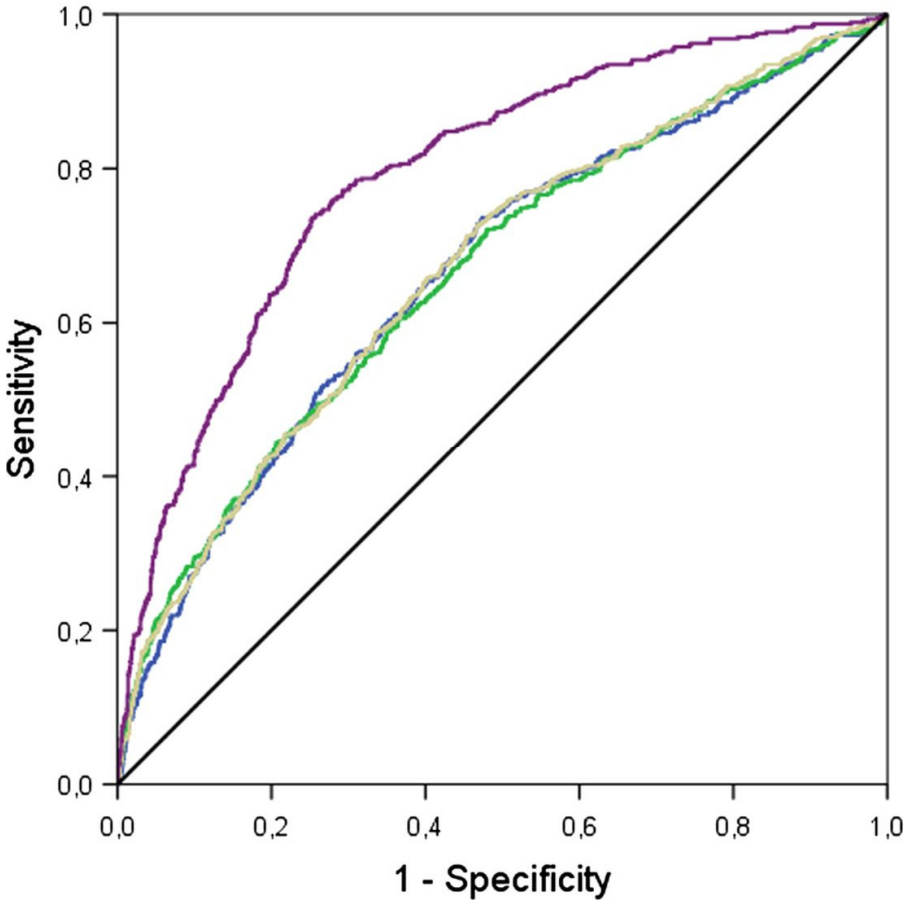
Predictor: ROA risk score based on age, sex, BMI, previous injury, pain in the entire leg, difficulty descending stairs, palpable effusion, fixed flexion deformity, restricted knee flexion range of motion, coarse crepitus

AUC 0.59 (0.49, 0.70)

Peat et al. (2010)

Individual risk prediction

Rotterdam study: RS-I (open population, 55+, n=3456)
Validation RS-II, Chingford study
Incident knee OA (KL ≥2) after 4-11 years



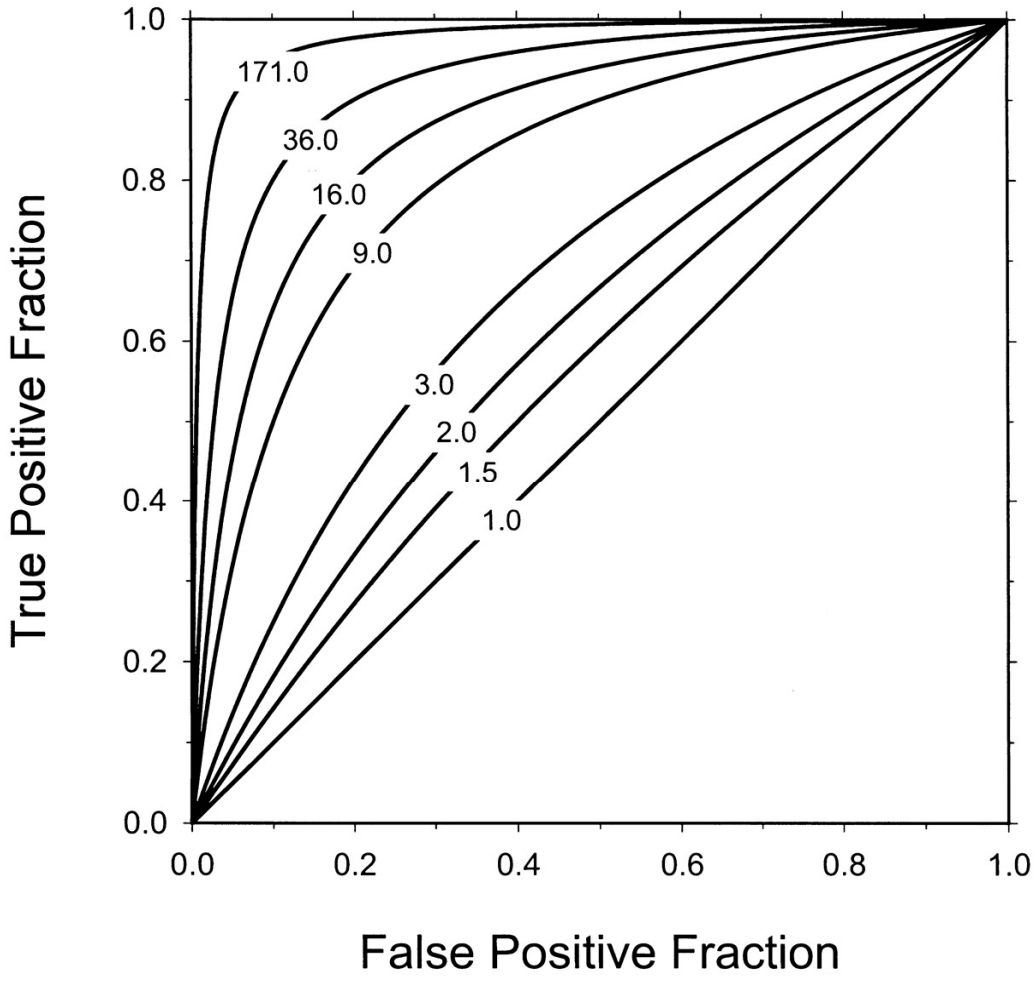
Gender, BMI, age
Gender, BMI, age, pain
Gender, BMI, age, pain, gen var
Gender, BMI, age, pain, gen var, KL1

OR pain most days last month
1.6 (1.2 to 2.2)
+2% variance explained

Kerkhof et al. (2014)

"Markers proposed for classifying or predicting risk in individual subjects must be held to a much higher standard than merely being associated with outcome. Their sensitivities and specificities must be shown to be adequate through appropriate statistical evaluations."

Pepe et al. (2004), p889



Interpretation

- Conventional clinical signs and symptoms (modestly) associated with MRI abnormalities and with future incident ROA are found in a minority of the population in pre-radiographic stages
- Individual risk prediction requires multiple variables. Thusfar conventional clinical signs and symptoms make small marginal contributions to prediction of individual risk of iROA.
- Traditional risk factors, exposure histories, and clinical variables remain important for stratification for preventive medicine. However, the majority of future cases of 'clinically significant OA' are likely to arise from the much more numerous subpopulation of persons in the low-medium strata
- Illness and disease states generally track themselves over time far more strongly than they predict each other

Redefining early symptom states

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Qualitative research

- Subthreshold symptoms: 'an awareness' of the knee, loss of confidence, needing to 'be careful'
- Intermittent symptoms, predictability of these
- Early emergence of adaptive behaviours
  - selection (e.g. performing some activities less often)
  - optimisation (e.g. greater advance planning of activities, including anticipatory analgesic use)
  - compensatory (e.g. modifying the way activities are performed)

Measurement instruments: KOOS, ICOAP, QUiKS

Roos et al. (1998); Gooberman-Hill et al. (2007); Hawker et al. (2008a); Maly & Cott (2009); Morden et al. (2009); Clarke et al. (2014); Gignac et al. (2002)

1) I have **no knee pain**

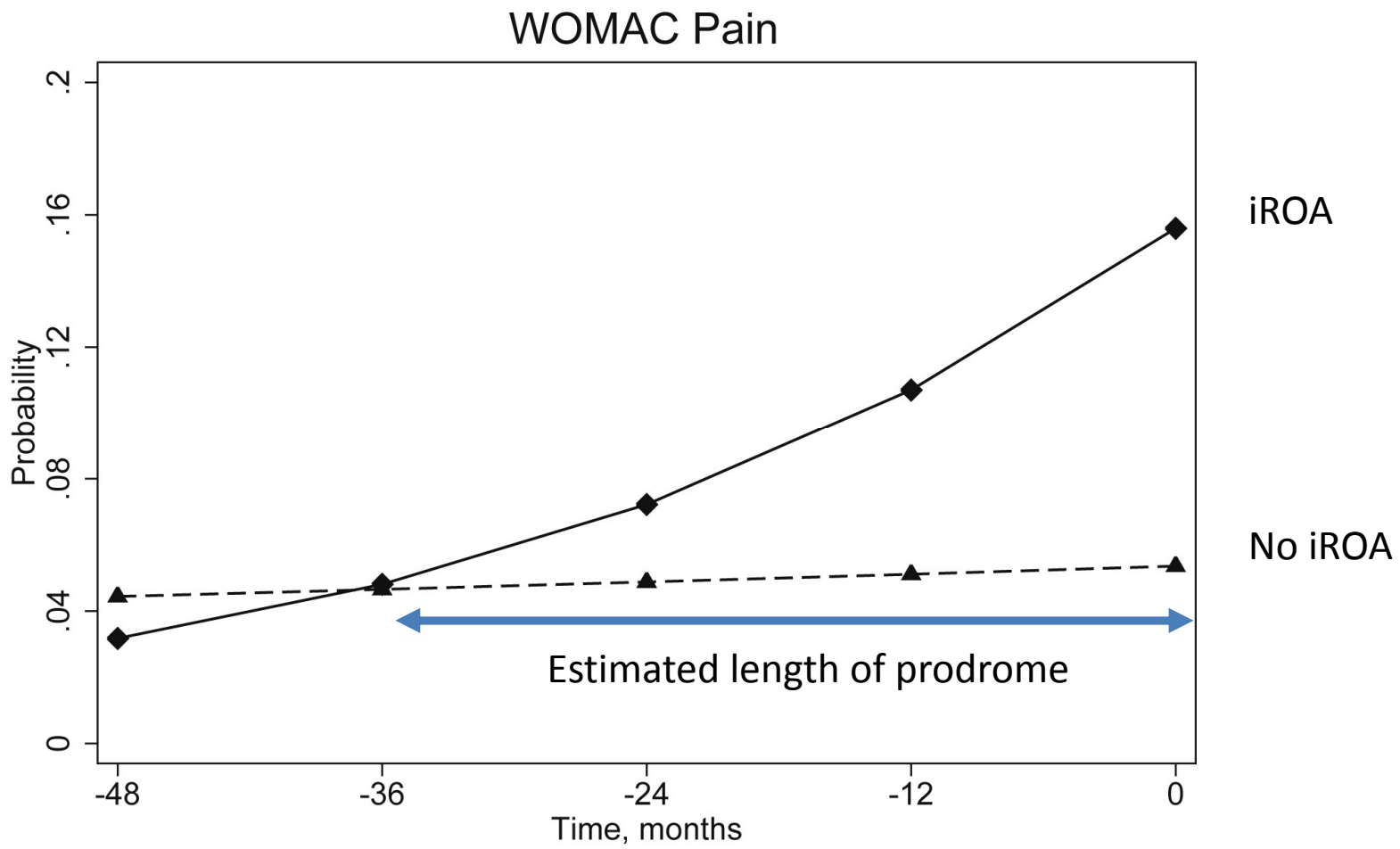
2) My pain is **predictable** (I know what brings it on) and usually sharp. It is usually **brought on by a trigger** (like an activity or movement) that has **kept me from high impact activities**, such as skiing, but has **not had much other impact** on my physical activities

3) My predictable pain comes more and more **with unpredictable** (comes when I don't expect it) **locking of knees or other knee joint symptoms.** The pain is **becoming more constant** and is **affecting daily activities**, such as walking and climbing stairs

4) My pain is **constant**, and is **dull and aching**. And, on top of this pain, I have **short episodes of often unpredictable intense pain** that leaves me **feeling exhausted**. Because of this pattern of pain, I am **avoiding a lot of social and recreational activities**

Rayahin et al. (2014) from Hawker et al. (2008b)

Symptom prodrome associated with the transition into ROA



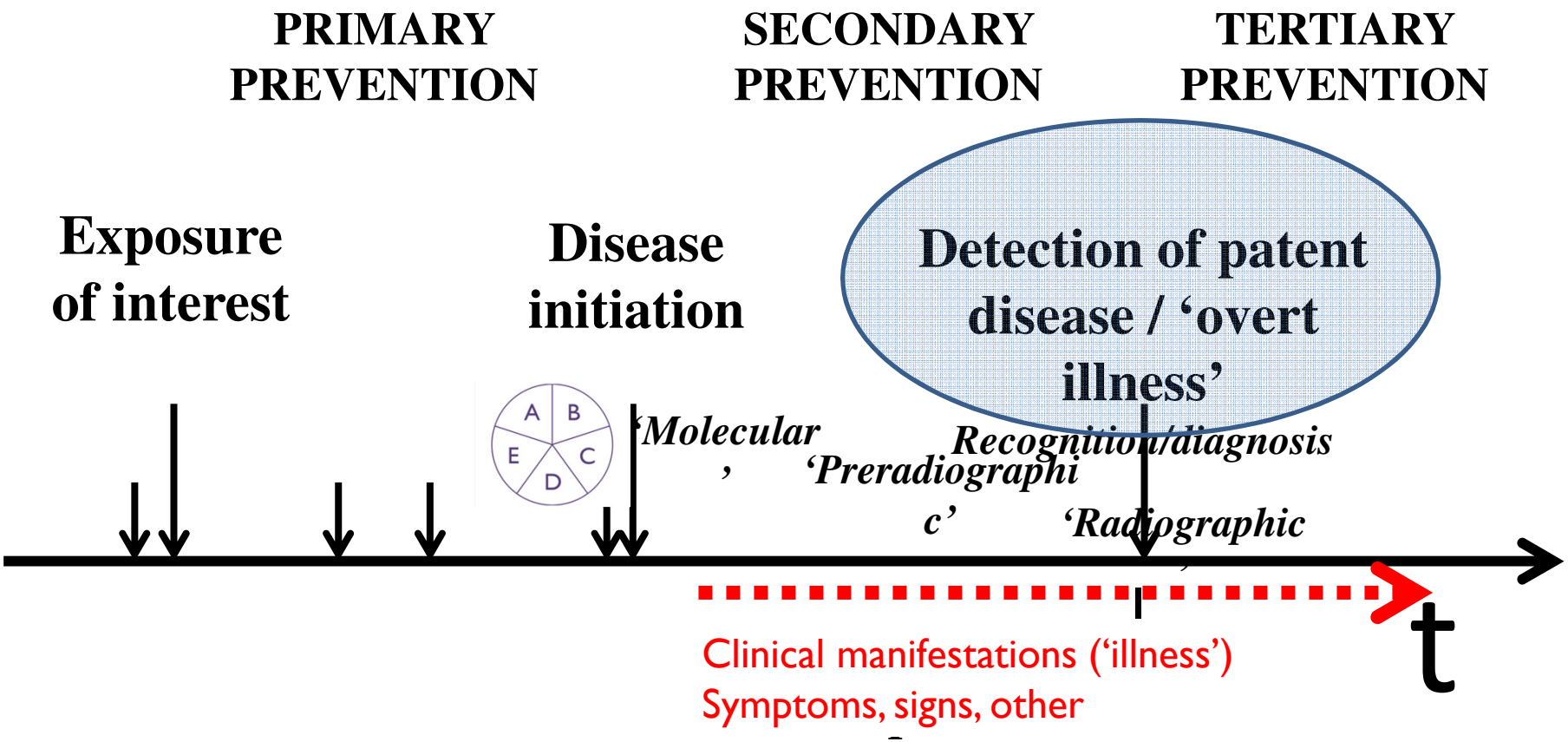
Case et al. (2015) [OAI data]

Item	Estimated length of prodrome (months)
Pain on stairs	40 (11, 69)
Pain on twisting/pivoting	39 (13, 64)
Pain on bending knee fully	38 (9, 69)
Swelling	35 (11, 59)
Awareness of a problem with the knee	30 (17, 43)
Frequent knee pain	29 (19, 39)
Pain on most days	28 (19, 38)

Case et al. (2015) [OAI data]

Interpretation

- A new wave of promising measurements and health state definitions. Given adequate psychometric properties (and conditional on licenses) they ought to be embedded in studies at every opportunity to build up the evidence base.
- A priority study is to describe the prognostically-relevant clinical profile of patients at the point when their problem is recognised by healthcare services


PRIMARY PREVENTION
SECONDARY PREVENTION
TERTIARY PREVENTION
Exposure of interest
Disease initiation
Detection of patent disease / 'overt illness'
A
B
C
D
E
'Molecular'
'Preradiographic'
Recognition/diagnosis
'Radiographic'
t
Clinical manifestations ('illness')
Symptoms, signs, other

- Of all 203 newly diagnosed cases of knee OA in 10 general practices (North Staffs, UK, 2010):
  - mean age: 68.7 years, range 39-97; 53% F

Total number of knee consultations in prior 10 years	n (%)
0	40 (20)
1	37 (18)
2	33 (16)
3	31 (15)
4-5	26 (13)
6+	36 (18)

Timing of most recent knee consultations prior to knee OA diagnosis	n (%)
No previous consultation	40 (20)
1-6 months	99 (49)
7-12 months	15 (7)
13-24 months	16 (8)
25-36 months	9 (4)
≥37 months	24 (13)

Yu et al, Submitted manuscript. [CiPCA data]

Interpretation

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- A new wave of promising measurements and health state definitions. Given adequate psychometric properties (and conditional on licenses) they ought to be embedded in studies at every opportunity to build up the evidence base.
- A priority study is to use these measures along with known risk factors and exposure histories to describe the (prognostically-relevant) clinical and disease profile of patients at the point when their problem is presented to recognised by (primary) healthcare services
- The point of entry into UK primary care is fuzzy and in many cases precedes formal diagnosis by several years.
- Patterns of pre-diagnosis consultations and risk factors within the EHR may form another practical method of defining early OA states

Concluding remarks

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- Selective; relative merits of preventive medicine vs other approaches to prevention? Evidence on the relative costs, effectiveness, harms of early vs late intervention; differences for different OA phenotypes?
- Disease, illness, presentation to healthcare: …sensible location of these in time
- Clinical manifestations evident in pre-radiographic phases and evidence of growth in the transition into ROA **but** often little/no signal from existing patient-reported measures
- Some promising measurements; greater application
- Conventional risk factors remain important for stratification

Concluding remarks

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- Distinction between levels of prevention more apparent than real
- Multiple transitions in episodic phasic development and progression?
- Keep risk stratification simple; integrate within EHR?
- Orientate to population-relevant outcomes, e.g. YLD, time spent in persistent pain, lost productivity and person-focussed (as opposed to disease-focussed) strategies
- Attempt to close rather than widen health inequities
- Involve patients and public

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Keele University

Thank you

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