Epidemiologische Erkentnisse aus der Verbundforschung, und ihr Nutzen für die Versorgung

Rudolf Kaaks
Deutsches Krebsforschungszentrum (DKFZ),
Heidelberg

Verbundforschung in der Epidemiologie

Consortial Research in Epidemiology

- **Creation of large research infrastructures (sample size):**
  - **Pooling projects**:
    - Re-analyses of existing data
    - Pooling of existing biobank resources
  - **Planned multi-centric studies**
  - **<u>Principal Aims</u>**:
    - estimation / replication of small effects (with account of multiple testing);
    - estimation of heterogeneity/interaction effects;
    - comprehensive risk modeling
- **Connection with basic (biologic & clinical) sciences:**
  - Medical Imaging; Diagnostics; Pathology
  - Diverse areas of “translation” both from / to basic research
    - e.g. molecular pathology, proteomics, population genetics
  - “Omics” as hypothesis-free approach for marker / risk factor discovery

The German National Cohort – basic design aspects

- **100,000 women & 100,000 men; 20-69 years, 18 recruitment centers**
- **Study levels:** general (N=200,000); intensified (N=40,000); MRI (N=40,000)
- **Baseline program:**
  - **Questionnaire modules**: physical activity, diet, smoking alcohol, psychosocial functioning, medical history, medication use,
  - **Physical / medical examinations:**

    CVD: arterial stiffness, ankle-brachial index, carotid intima media thickness, ECG, 3D-echocardiography & MRI, hypertension

    Respiratory: spirometry (lung function), exhaled FeNO (airway inflammation)

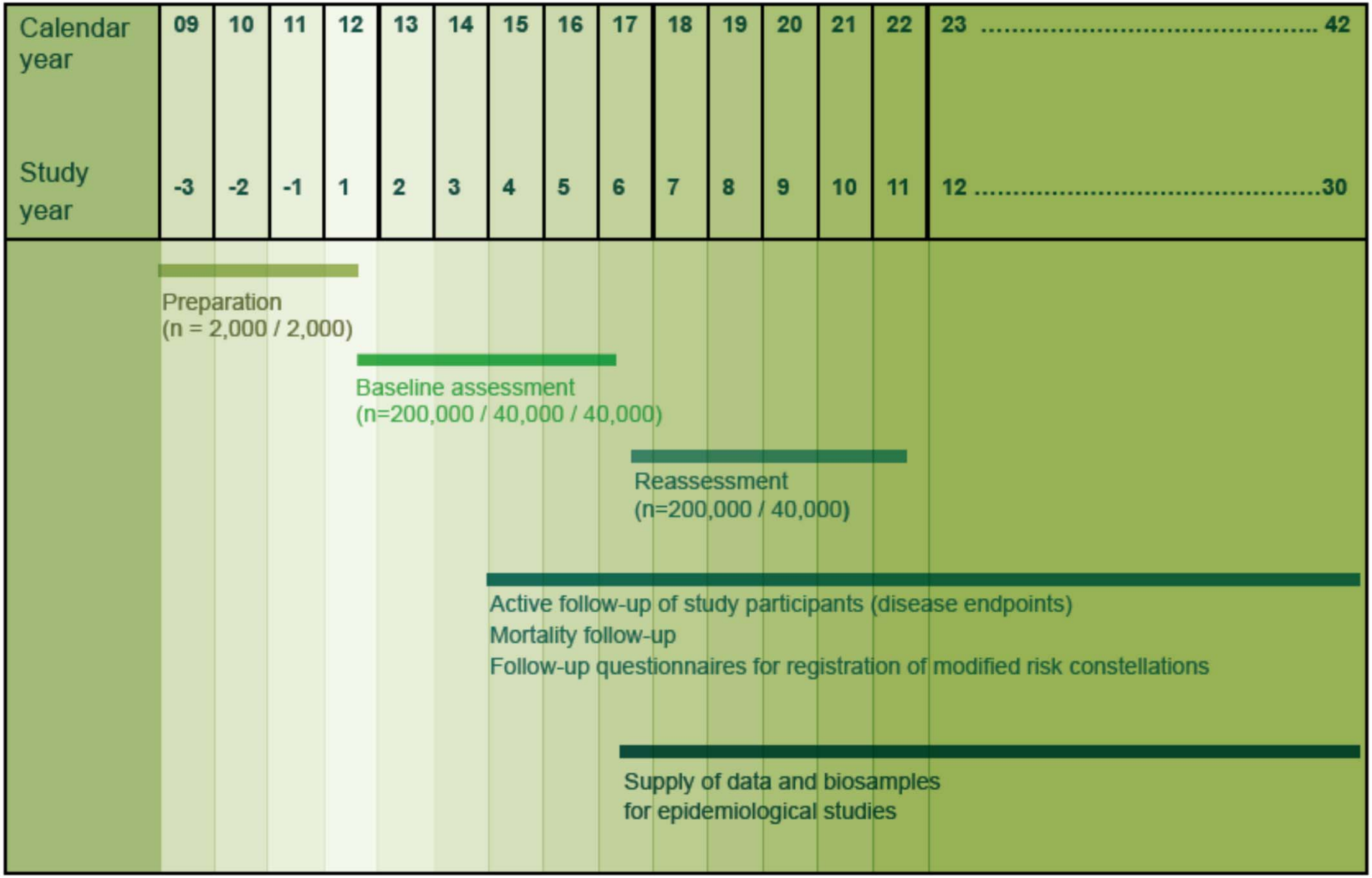
    (Pre-)Diabetes: fasting glucose, OGTT, AGE-products (skin), retinopathy

    Neuropsychiatric: Cognitive function tests (MCI), olfactory tests, brain MRI

    Musculoskeletal: osteoarthritis (MRI); rheumatoid arthritis (clinical exam); osteoporosis (DXA)
  - **Collections of Biomaterials:** blood, urine, saliva, stool, tumor tisssues
- Active follow-up + record linkages: CVD, diabetes, Cancer, Neurologic & psychiatric diseases, respiratory diseases, infectious diseases

The German “National Cohort” areas of recruitment and participating centers

The German “National Cohort” – overall time plan



Prevention Perspectives

- **"Primary":** Identification of common, and avoidable causes of disease
  Mostly: Recommendations to the **general** population

  Identification of high-risk individuals for intensified preventive treatment:
  - lifestyle intervention (under medical surveillance)
  - chemoprevention (e.g., finasteride, SERMs, sulindac, celecoxib, metformin, …)
  - (intensified) screening surveillance

- **"Secondary"**: Development & evaluation of methods for early diagnosis;
  → To improve chances of cure / increase survival

- **"Tertiary"**: Identification of (modifiable) determinants of disease progression

  → Overlap with primary risk factors for disease (e.g., excess weight; genetic factors)

Lessons learned from large-scale prospective studies
Example: Estrogens (+ Progestins) and Breast Cancer

- Use of combined (E+P) HRT transiently increases breast cancer risk
  - Time-related association between strong reductions in HRT use since …. and breast cancer incidence rates (USA, Europe)
- ERT increases endometrial cancer risk, whereas combined HRT does not, or even reduces risk.
- Postmenopausal serum estrogens increase risks of breast (especially of ER+) and endometrial cancer
- Use of selective estrogen receptor modulators (SERMS – e.g. tamoxifen, raloxifene):
  - Adjuvant therapy for breast cancer
  - Breast cancer **chemoprevention**; to be balanced against risks (e.g., endometrial cancer, stroke).
- **Risk models** to identify women who may mostly benefit from SERMs (risk of breast cancer vs. endometrial cancer, stroke)

Risk (Prediction) Scores

- **Self assessment (basic data)**
  - e.g., German Diabetes Risk Score; “Breast Cancer Risk Assessment Tool [BRCAT]”
- **Scores integrating clinical examinations:**

  e.g., Framingham Risk Function; Cardiovascular Risk Score;
  National Cholesterol Education Panel Adult Treatment Panel (ATP-III);
  BRCAT + mammography

- **Scores integrating serum biomarkers**

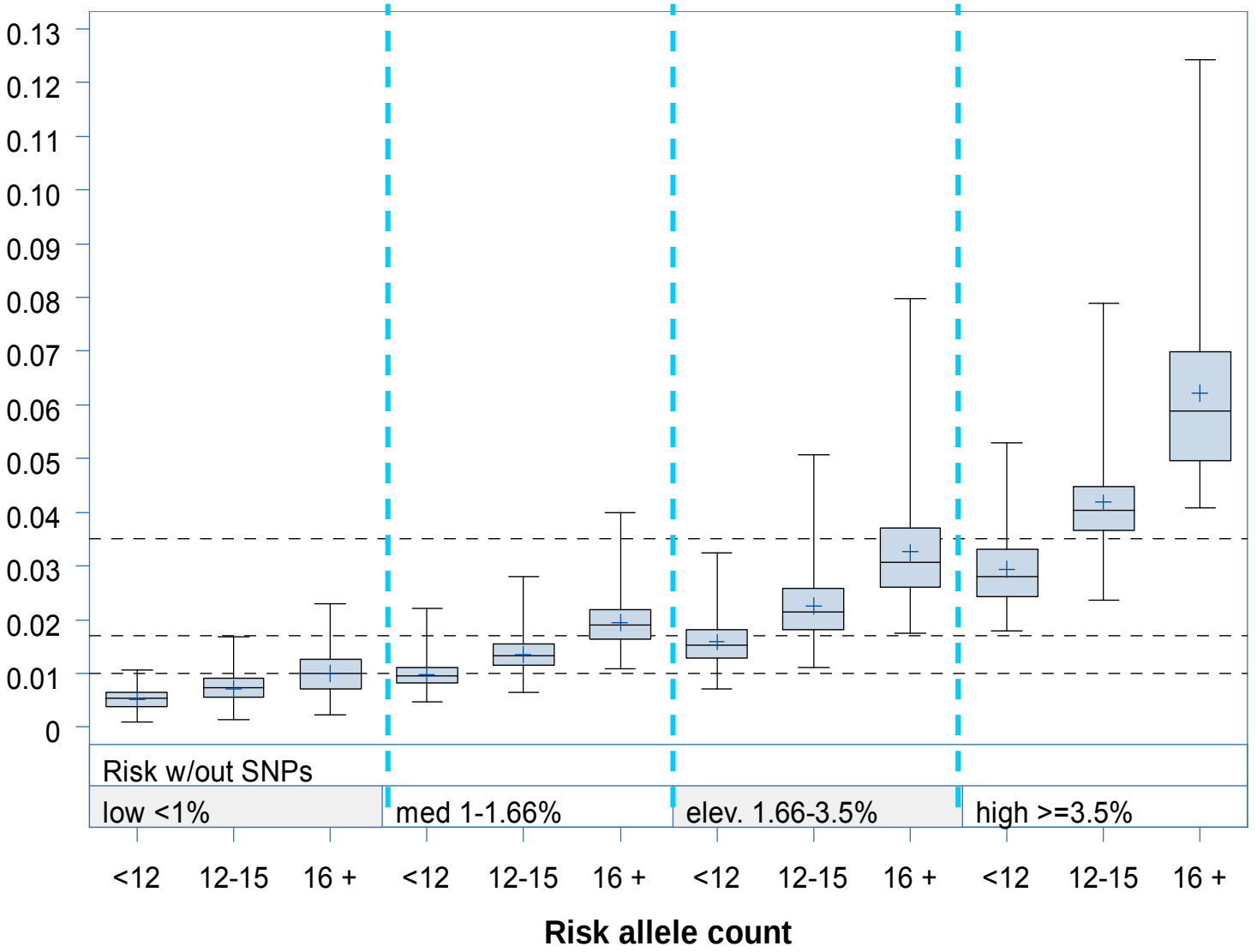
  e.g. “Framingham Risk Score”, “SCORE”, “FINRISK”, “MORGAM”, “Reynolds” and others for estimation of CVD risks

  various models also for diabetes

- **Scores integrating genetic markers**

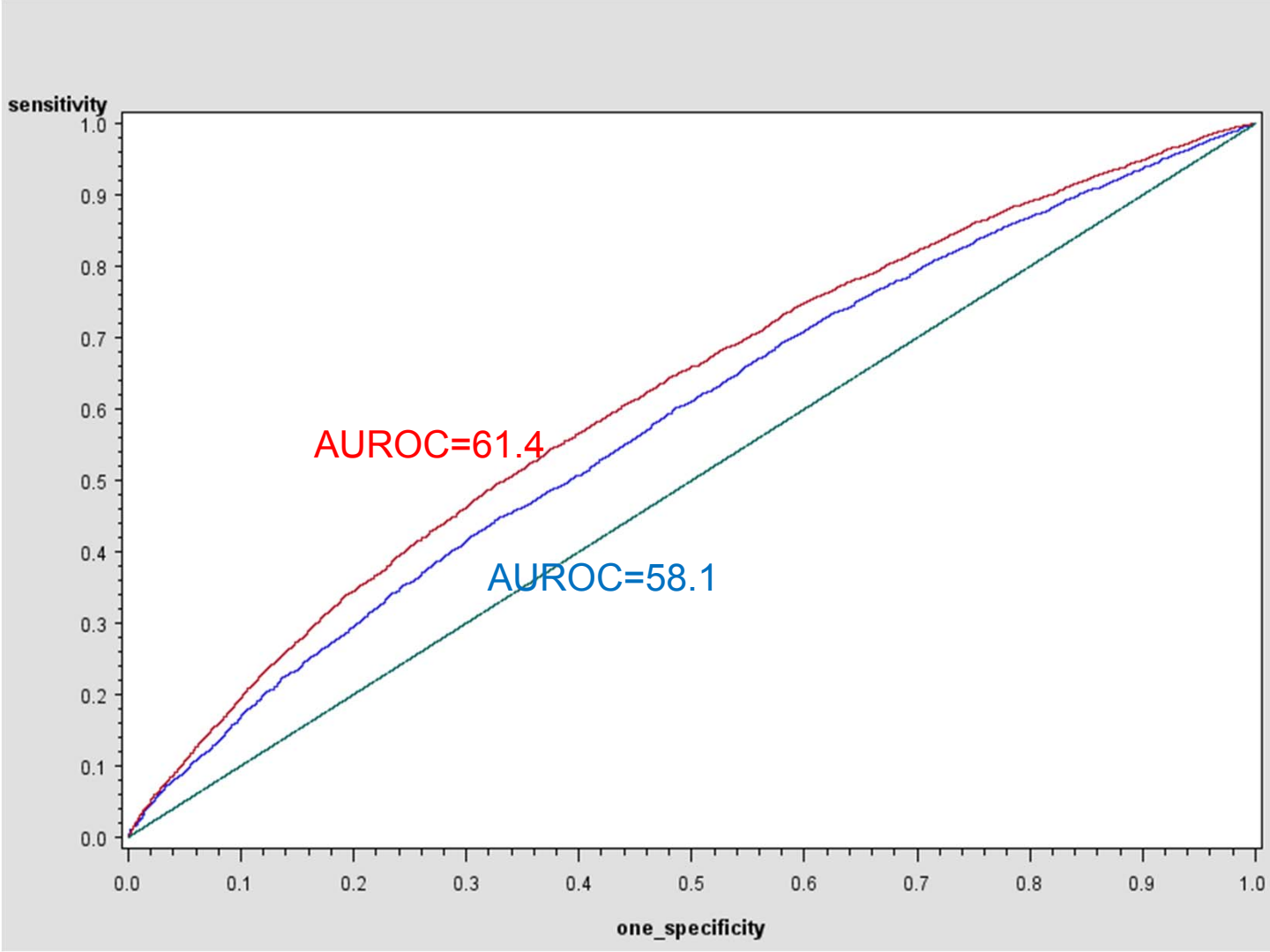
<u>Ultimate objective</u>: Estimation of <u>absolute risks</u>

Absolute risk of breast cancer risk by"traditional" covariate risk score and by genetic score based on 14 SNPs (#risk alleles carried)



Hüsing et al., MS in preparation

Discrimination of a breast cancer risk model based on traditional risk factors information alone, or augmented and with 14 SNPs

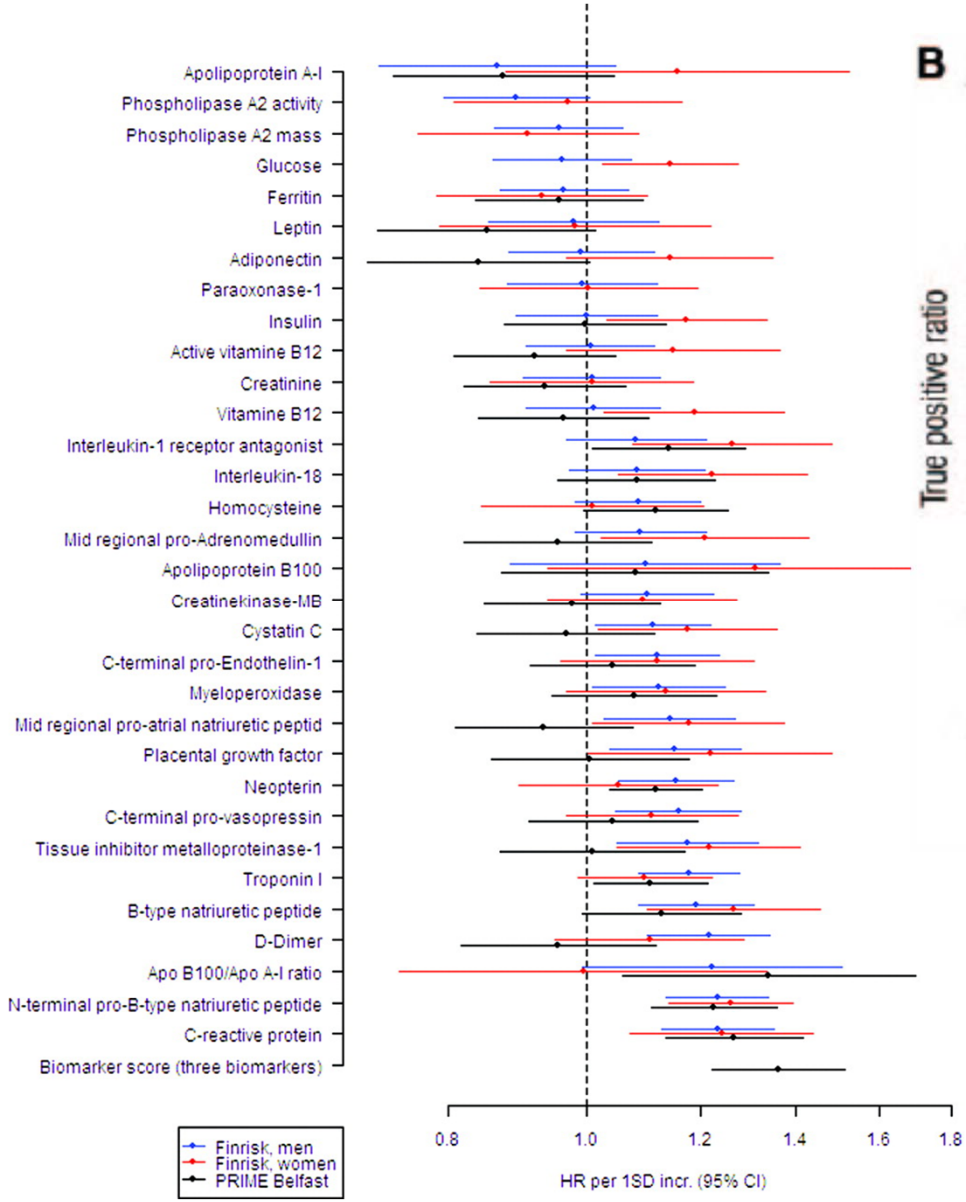


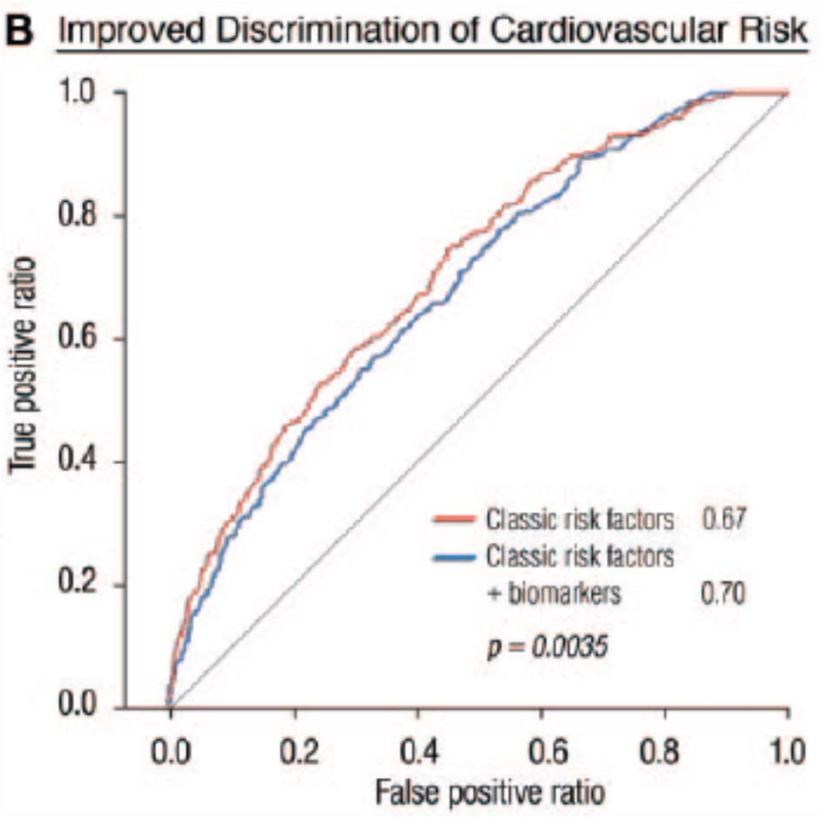
Hüsing et al., MS in preparation

Risk Biomarkers in Cardiovascular Disease

- ***Coagulation:*** Fibrinogen, D-Dimer
- ***Blood Lipids:*** Small dense lipoproteins, Apolipoprotein A, Apolipoprotein B, Apolipoprotein E, Lipoprotein(a), Lipoprotein-associated Phospholipase A2, paraoxonase-1
- ***Oxidative stress, antioxidants:*** Homocysteine, Myeloperoxidase, vitamin B12
- Uric acid, Alanine aminotransferase, Gamma glutamyltransferase
- ***Inflammation:*** White Blood Cell Count, C-Reactive Protein, Macrophage/Monocyte Colony Stimulating Factor, Monocyte Chemoattractant Protein-1, Interleukins 1, 1b, 6, 10, Transforming Growth Factor *β1*, Tumor Necrosis Factor-*α*, Osteoprotegerin
- ***Oxidative and Nitroxidative Stress:*** Nitrotyrosine, Myeloperoxidase, Neopterin
- ***Myocardial Injury and Ischemia:*** Cardiac Troponins
- ***Myocardial stress:*** Natriuretic Peptides, Interleukin-1, Interleukin-6, ST-2, Adrenomedullin, Midregional Pro Adrenomedullin
- ***Neurohormonal Activation:*** Norepinephrine, Endothelin-1, Big Endothelin-1
- ***Renal Function:*** Creatinine Clearance, Microalbuminuria, Cystatin C
- ***Metabolic markers:*** insulin, glucose, ferritin, leptin, adiponectin

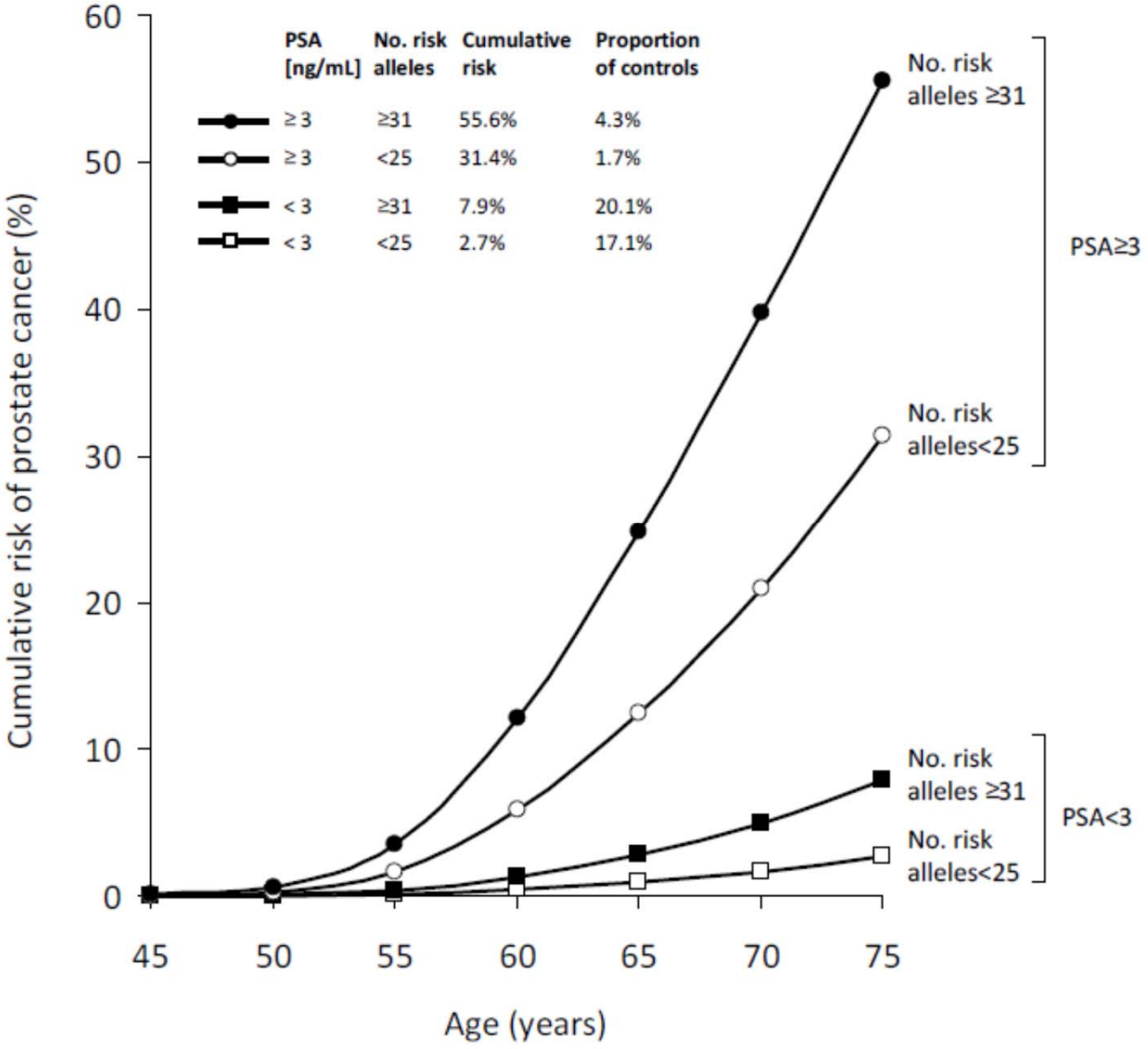
Hazard ratios of cardiovascular events for biomarkers





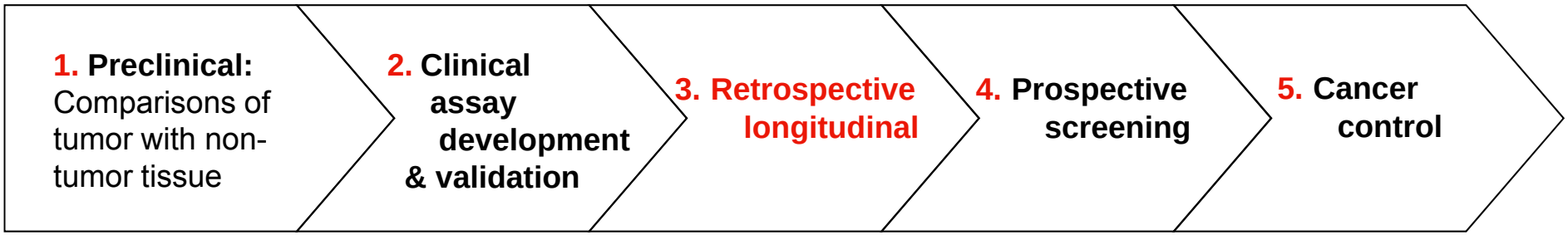
Blankenberg et al., Circulation 2010

Cumulative risk of prostate cancer up to age 75, for categories of PSA and genetic risk score (nr of risk alleles for 33 SNPs)



Phases of development of biomarkers for early cancer detection

Pepe et al., JNCI, 2001



1. Preclinical, Exploratory	Identifying promising markers
2. Clinical Assay Development	Clinical Assay Detects Established disease; Development of a test that can be used in practice
3. Retrospective Longitudinal (Studies of Stored Specimens)	Biomarker detects disease before it becomes clinical (lead time estimation); Definition of “screen positive” rule.
4. Prospective Screening	Evaluation of extent of detected disease & False Referral Rates
5. Cancer Control	Impact of screening on reducing the burden of disease on the population is quantifies

Evaluation of markers for early detection
Phase 3 – Retrospective Longitudinal Repository Studies

Primary Aims

- To evaluate, as a function of time before clinical diagnosis, the capacity of a marker to detect preclinical disease → **estimation of lead time**
- To define criteria for a positive screening test in preparation for phase 4

Secondary Aims

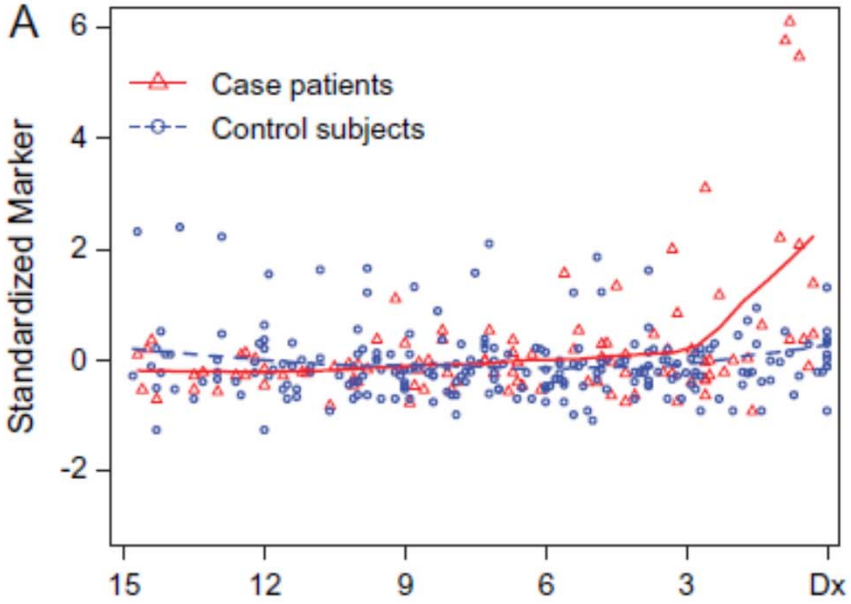
- To explore the impact of covariates on the discriminatory abilities of the biomarker before clinical diagnosis
- To compare markers, with a view of selecting those that are most promising
- To develop algorithms for screen positivity based on combinations of markers
- To determine a screen interval for phase 4, if repeated screening is of interest

Pepe et al., *JNCI*, 2001

Assessing lead time of selected ovarian cancer biomarkers – a nested case control study within the CARET cohort.

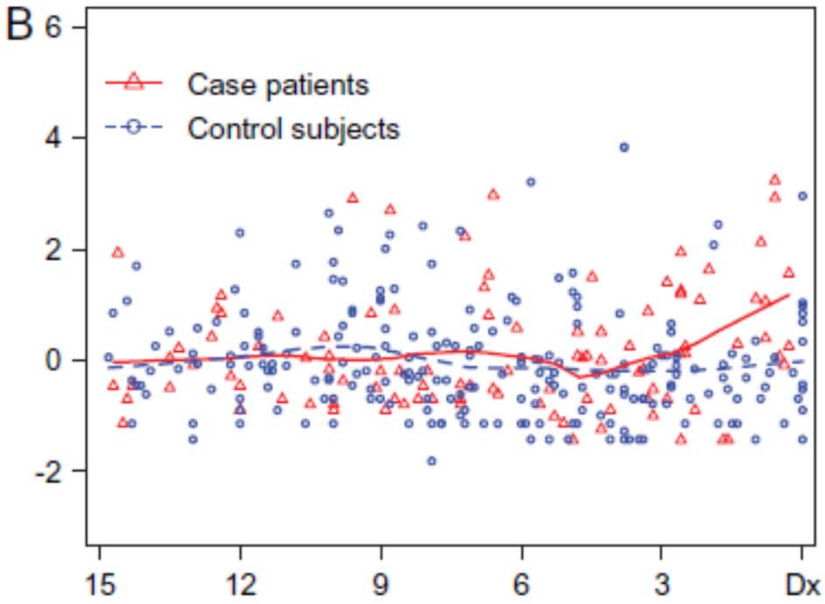
Lowess curves of standardized marker levels by time before diagnosis

CA125



Time before diagnosis, years

HE4



Time before diagnosis, years

Anderson et al., JNCI 2010;102:26-38

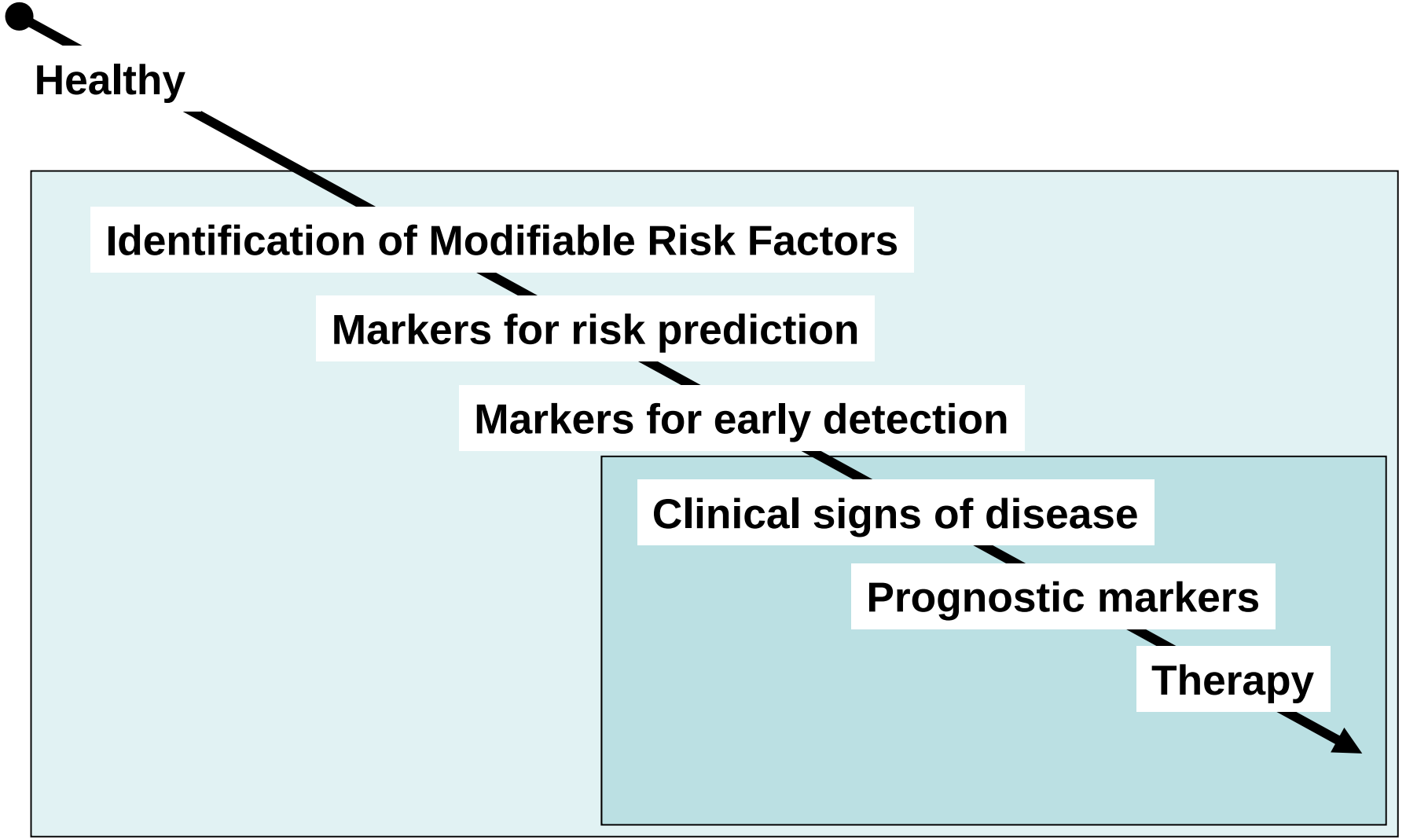
Summary (i)

Improving risk prediction:

- **Improving discrimination** (using combined methods)
  - Classical risk factors & medical examinations
  - Genetics
  - Biomarkers:
    - "conventional" (hypothesis/candidate based)
    - "OMICs": metabolomics, epigenomics, proteomics, ….
  - Imaging
  - Use of repeat measurements in time (ex.: PSA velocity, CA125 change)

- **Improving absolute risk prediction (calibration):**
  - prospective studies + population survey for evaluation of risk factor prevalence

The National Cohort (Germany) – Translational Research Objectives



Summary (ii)

Improving knowledge of disease sub-types, and etiology:

- Dissecting etiologies of disease subtypes:
  - e.g., tumours, diabetes
- Linking studies of etiologic factors to prognostic studies in patient cohorts.

Thank you for attention !

Personalized prevention approaches (examples)

- **Cancer**
  - Development of risk models / screening tools
  - Eligibility for screening / determination of screening intensity
  - Eligibility for Chemoprevention: e.g., finasteride, SERMs, COX2 inhibitors, metformin (& analogues)

- **Diabetes**
  - Elucidating diabetes heterogeneity (etiology, diagnostics) → personalized glycemia management)
  - Lifestyle intervention

- **Cardiovascular**
  - Lifestyle intervention
  - Treatments: anti-hypertensive (diuretics); LDL-cholesterol lowering (HMGCA reductase inhibitors); aspirin / platelet inhibitors; β-blockers;

Prospective Cohort Studies – advantages & constraints

Advantages:

- Less susceptibe to biases: selection, recall, “inverse causation”
- Repeat measurements over time:
  - risk factors (cumulative + changes);
  - Intermediate (pre)clinical outcomes / risk factors
- Study of multiple disease outcomes in parallel, or in combination (multi-morbidity);
- Studies of mortality, conditions with high fatality rates or incapacity (dementias, stroke, MI,..)
- Suitable for competing risk modeling
- More suitable for modeling of absolute risks

Constraints:

- Cohorts most be very large, and hence are expensive
- Representativeness of study participants us be balanced against needs of long-term study participation.
- (Very) Long study duration

Epidemiology: from “cottage industry” to “BIG” science

THE CHANGING FACE OF EPIDEMIOLOGY

Editors' note: *This series addresses topics that affect epidemiologists across a range of specialties. Commentaries are first invited as talks at symposia organized by the Editors. This article was originally presented at the 2006 Congress of Epidemiology in Seattle.*

The Evolution of Epidemiologic Research

From Cottage Industry to “Big” Science

Robert N. Hoover

Epidemiology, 2007;Vol 18, No. 1

Enhancing the Feasibility of Large Cohort Studies

Teri A. Manolio, MD, PhD

Rory Collins, FMedSci

To Centralize or Not

Centralized

entical fashion throughout the

JAMA, Vol 2010;304, No. 20

COMMENTARY

The Evolution of Population Science

Advent of the Mega Cohort

J. Michael Gaziano, MD, MPH

observation, he noted a dramatic difference in the rate of puerperal sepsis between obstetric wards and determined

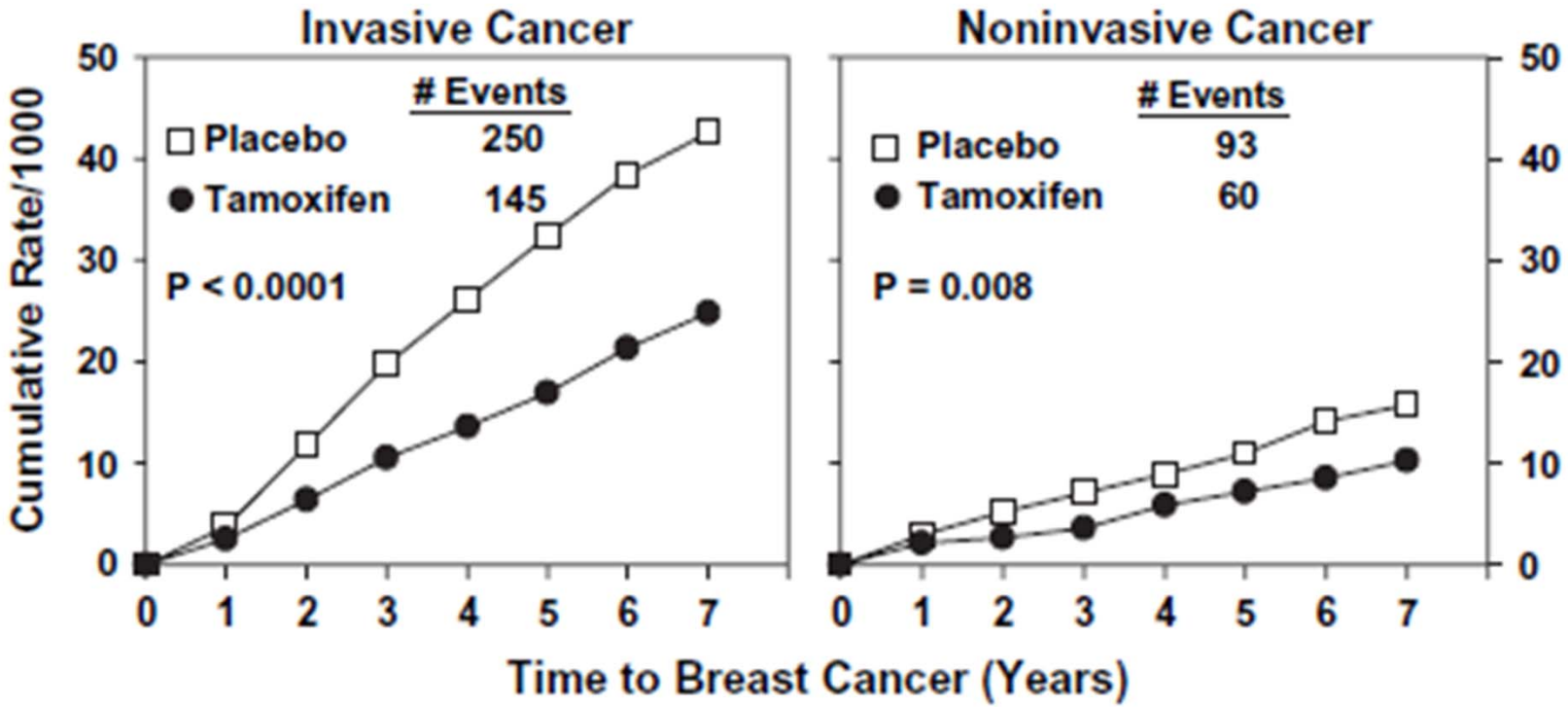
“Nutzen für die Versorgung”

Lessons learned from large-scale prospective studies

Example (2): Glucose/Insulin metabolism and cancer risk

- Excess weight ←→ plasma insulin / glucose / diabetes
  ←→ cancers of the colon, endometrium, kidney, pancreas, (+ breast)
- Metformin use among diabetics ←→ lower risk of colon cancer
- Metformin (and analogues): glucose + insulin lowering, but also activator of AMPK (central in regulating cellular energy metabolism)
- Intervention trials of metformin (+ analogues) to reduce cancer recurrence
- Perspective: Possible chemoprevention on population level

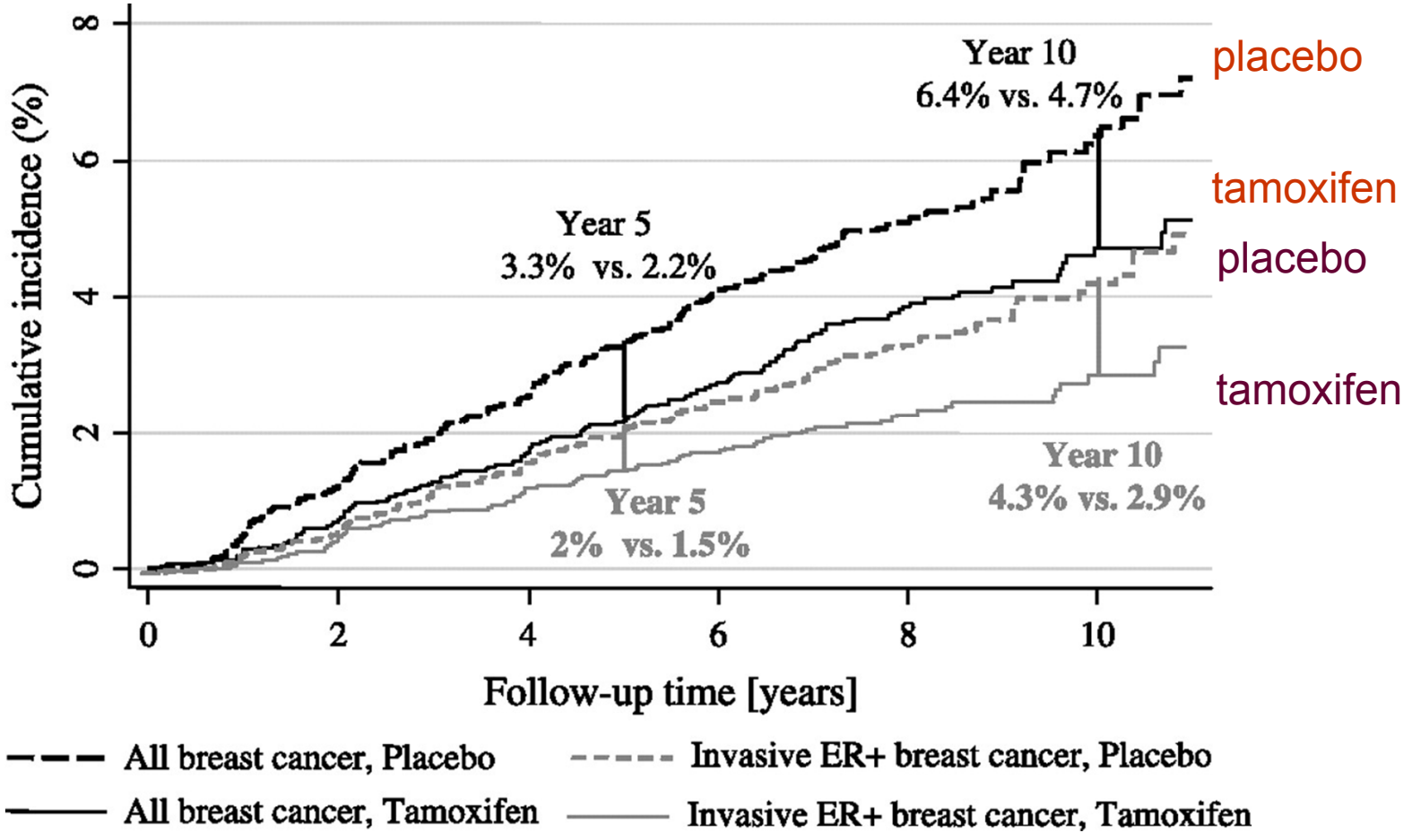
NSABP P-1 trial – cumulative rates of breast cancer per 1000 study participants, by treatment group



Fisher et al, JNCI, 2005

National Surgical Adjuvant Breast and Bowel Project Breast cancer Prevention Trial

Cumulative incidence for all breast cancers and invasive ER-positive breast cancers according to treatment arm; IBIS-I Trial



Cuzick, J. et al. J. Natl. Cancer Inst. 2007 99:272-282

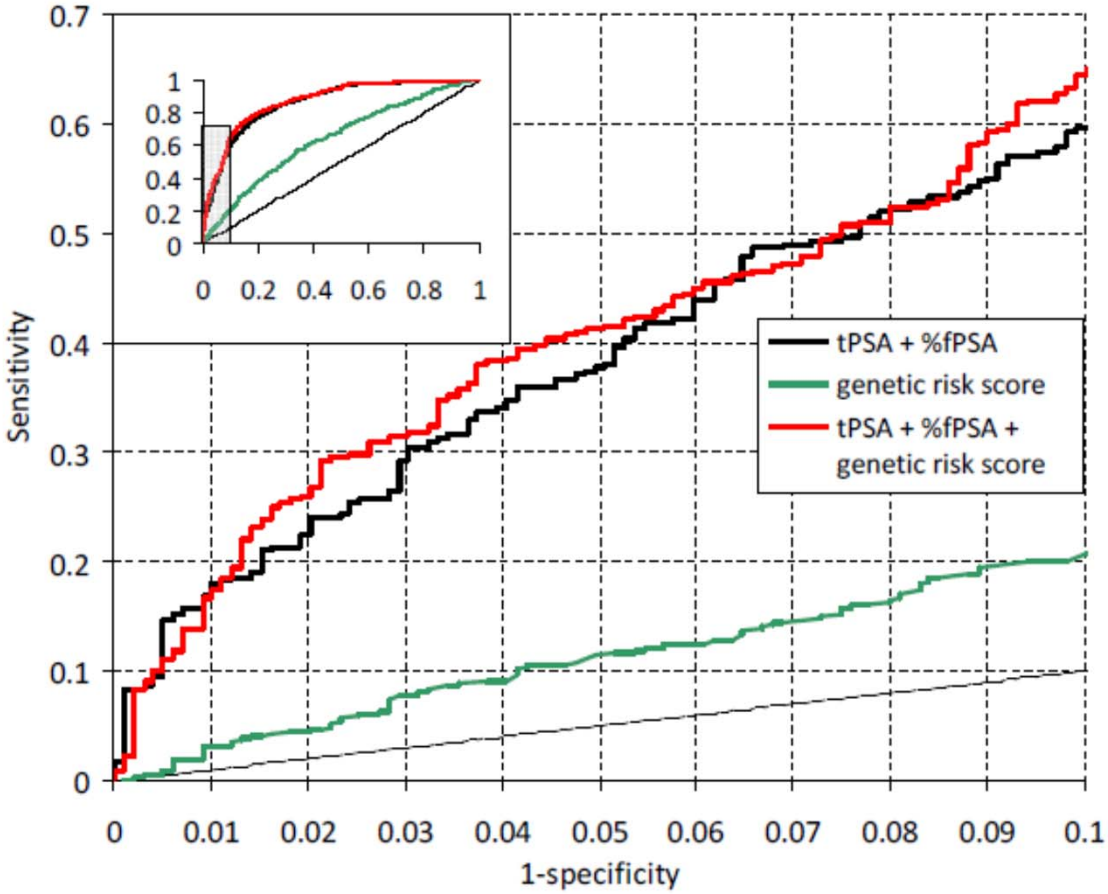


Figure 3 | ROC curves for prediction of overall prostate cancer diagnosis using three risk models, limited to data resulting in a specificity above 0.90. All risk models included demographic variables describing age and year of recruitment; tPSA denotes total PSA; %fPSA denotes percent free PSA; the genetic risk score was defined as the number of risk increasing alleles carried by an individual. The risk allele was defined based on the findings from the original studies (eTable 1).

Prospective cohort (Biobank) studies – a platform for multidisciplinary research

Prospective cohort with Biobank(s)
Blood, Urine, Saliva, Stool, Tissues

Conventional (hypothesis-based) biomarkers of risk
- diet / nutrition
- metabolism
- infection
- immune function

Candidate markers for early Detection
- Proteins
- Circulating tumor cells
- Mutated / methylated DNA
- Immune factors

Omics Technologies
- Genomics
- Epi-genomics
- Transcriptomics
- Proteomics
- Metabonomics
- Microbiomics

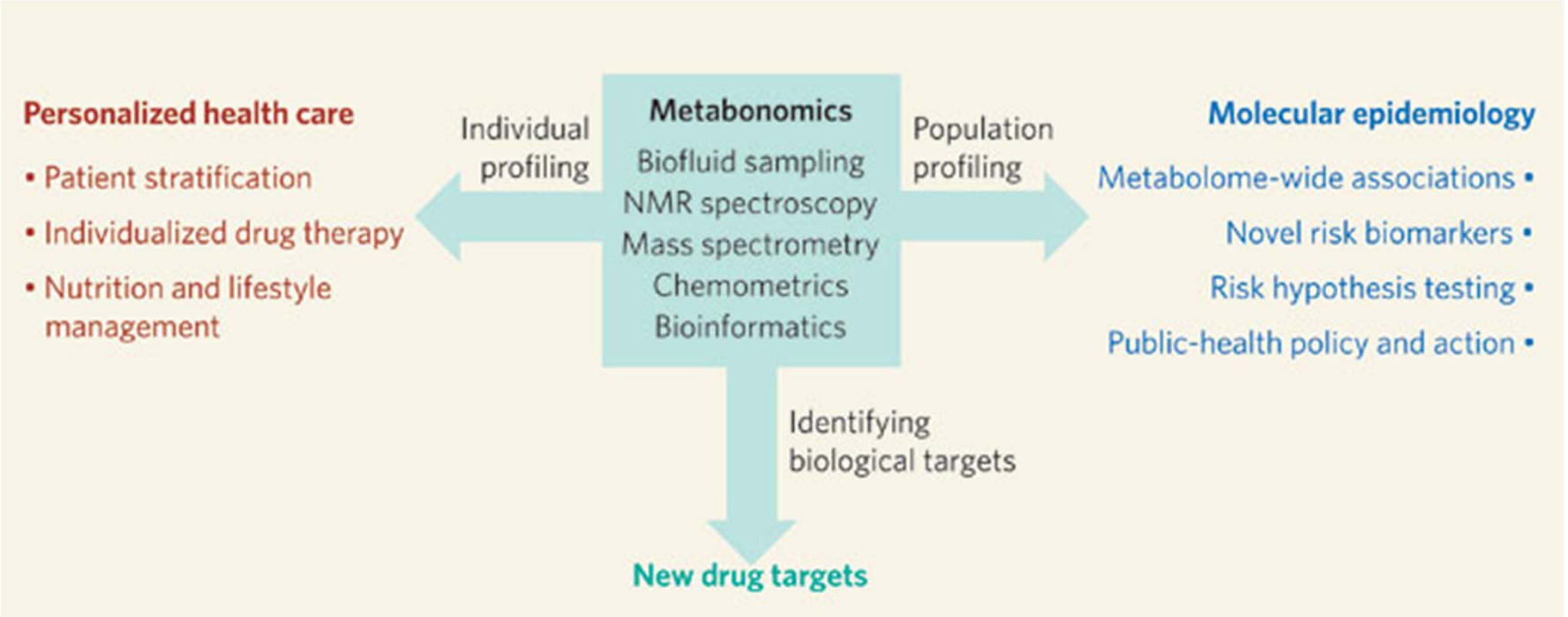
Selection of predictive biomarkers

Biomarkers Added to Baseline Model	c-Index			IDI	
	New	Difference	*P*	Value	*P*
FINRISK 97 men*					
C-reactive protein	0.8199	0.0031	0.1123	0.0100	0.0008
NT-proBNP	0.8200	0.0032	0.0716	0.0157	0.0002
Troponin I	0.8213	0.0045	0.0028	0.0077	0.0002
FINRISK 97 women†					
C-reactive protein	0.8772	0.0015	0.4689	0.0068	0.0685
NT-proBNP	0.8831	0.0073	0.0023	0.0194	<0.0001
Troponin I	0.8766	0.0009	0.3950	0.0037	0.0086
PRIME Men Belfast‡					
C-reactive protein	0.6798	0.0140	0.0440	0.0085	0.0032
NT-proBNP	0.6772	0.0114	0.0427	0.0080	0.0017
Troponin I	0.6697	0.0039	0.2039	0.0019	0.1610

*c-Index baseline=0.8168; †c-index baseline=0.8757; ‡c-index baseline=0.6658.

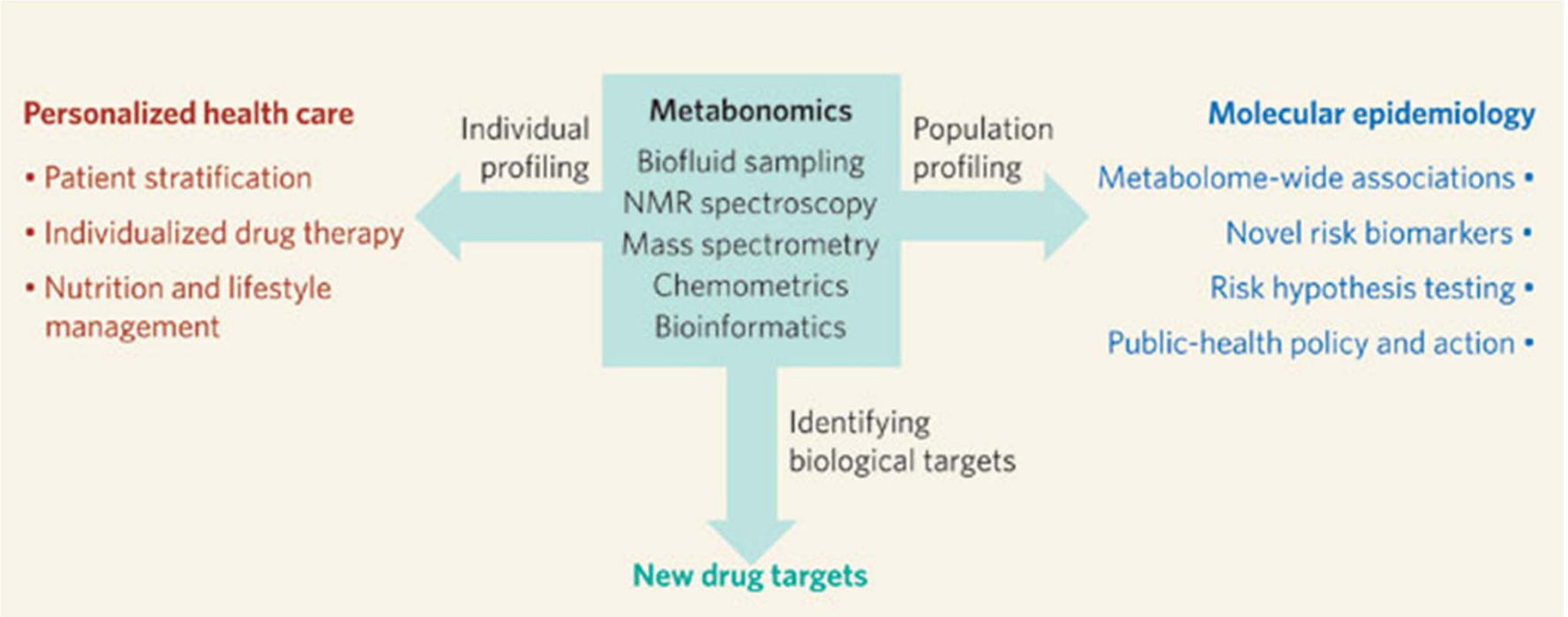
Blankenberg et al., Circulation, 2010

Metabonomics – a tool for personal medicine



From: Nickolson JK, Nature, 2008

Metabonomics – a tool for personal medicine



From: Nickolson JK, Nature, 2008

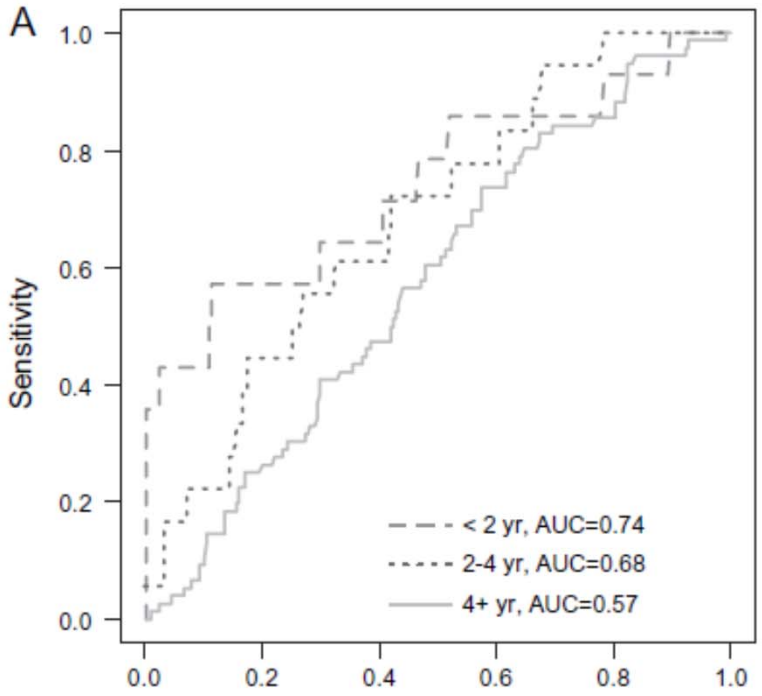
Similar arguments for:

- Transcriptomics (blood lymphocytes)
- Epigenomics
- Proteomics

Assessing lead time of selected ovarian cancer biomarkers – a nested case control study within the CARET cohort.

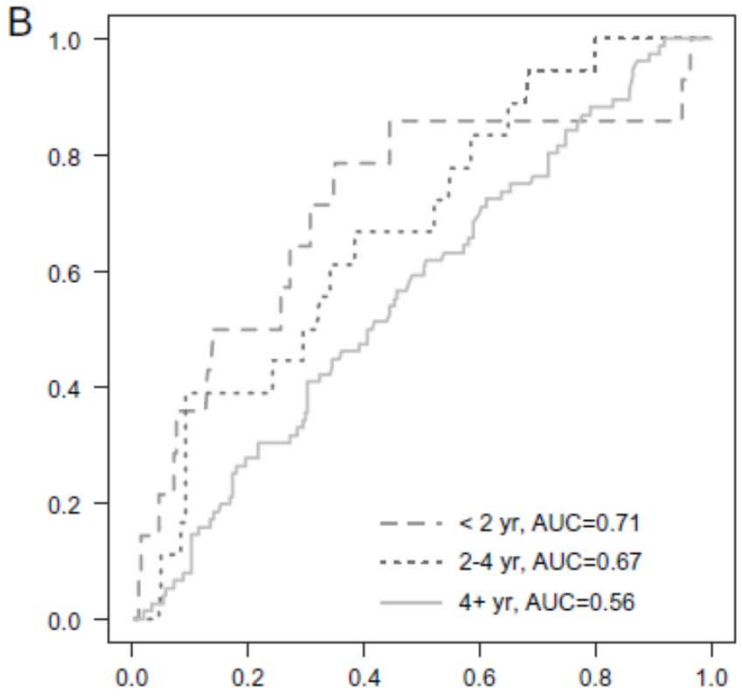
Receiver operating characteristics curves, by time before diagnosis

CA125



Time before diagnosis, years

HE4



Time before diagnosis, years

Anderson et al., JNCI 2010;102:26-38