MANCHESTER 1824
The University of Manchester

CfMR
Centre for Musculoskeletal Research

Preventing psoriatic arthritis: targeting interventions in high risk groups

John Bowes

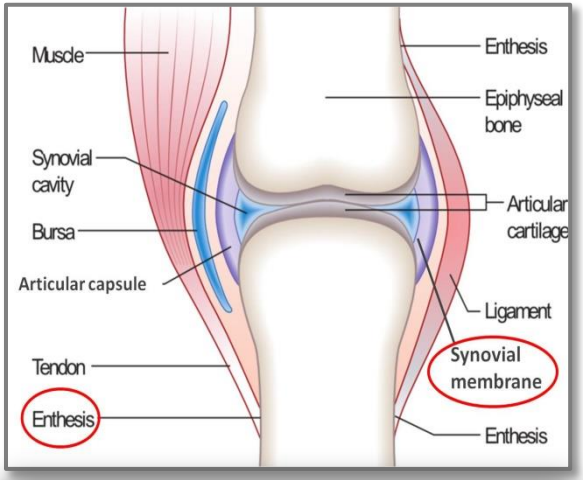
ARTHRITIS RESEARCH UK

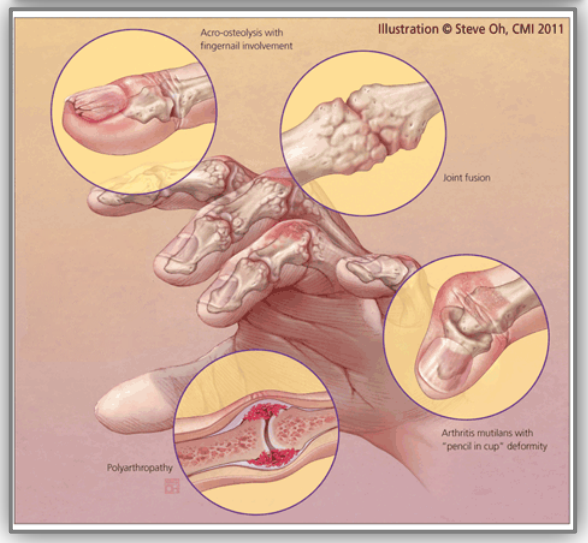
NHS
National Institute for Health Research

MANCHESTER 1824
The University of Manchester

Psoriatic Arthritis

- Arthritis associated with psoriasis
- Prevalence of PsA in patients with psoriasis ~30% (UK)
- Heterogeneous disease
  - peripheral arthritis
  - axial disease (sacroiliitis)
  - dactylitis
  - enthesitis
  - nails



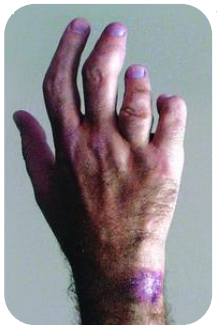


MANCHESTER 1824
The University of Manchester

Impact on Quality of Life

Psoriasis

- Psoriasis precedes PsA
- Physical and psychological burden



Arthritis and enthesitis

↑ disability

↓ physical and social function

↓ work productivity

Comorbidities

- Increased prevalence
- •CVD, metabolic syndrome, obesity, depression ....
- higher than psoriasis alone

Predicting PsA

- Typically psoriasis precedes PsA
- Represent a high risk group
  - Prevalence of PsA ~30%
  - Joint lesions ~50%
- Scenario for disease prediction
- **Mitigate** impact of PsA

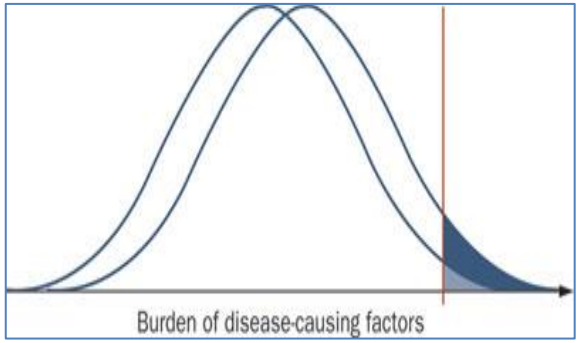
MANCHESTER 1824
The University of Manchester

Predicting PsA

- Common complex disease

    1. Genetic risk factors
    2. Environment risk factors
    3. G+E = liability

- Impact: need to identify PsA-specific risk factors



MANCHESTER 1824
The University of Manchester

Aim:

Identify risk factors that can help differentiate PsA from cutaneous-only psoriasis

Benefits:

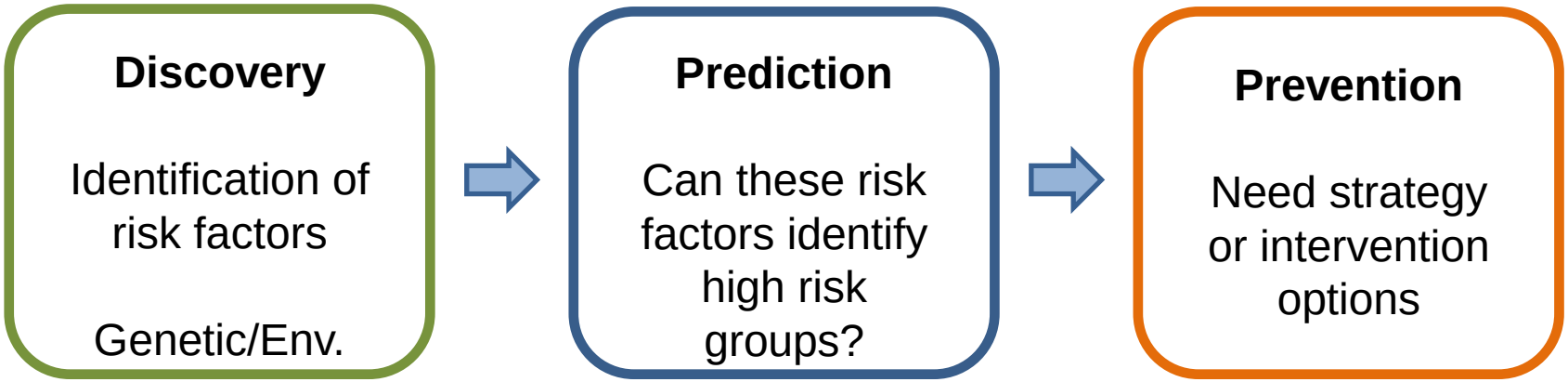
- Improved diagnosis

  Delay in diagnosis → worse outcome

- Preventing disease

MANCHESTER 1824
The University of Manchester

Pathway to prevention



MANCHESTER 1824
The University of Manchester

Pathway to prevention

Discovery

Identification of risk factors

Genetic/Env.

Prediction

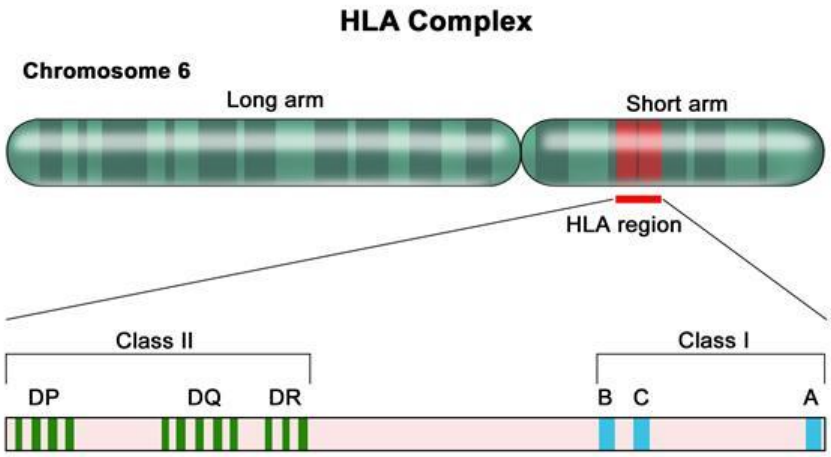
Can these risk factors identify high risk groups?

Prevention

Need strategy or intervention options

MANCHESTER 1824
The University of Manchester

Major Histocompatibility Complex



Importance

- Major genetic risk factor
- Enriched for immune genes
- HLA – antigen presentation

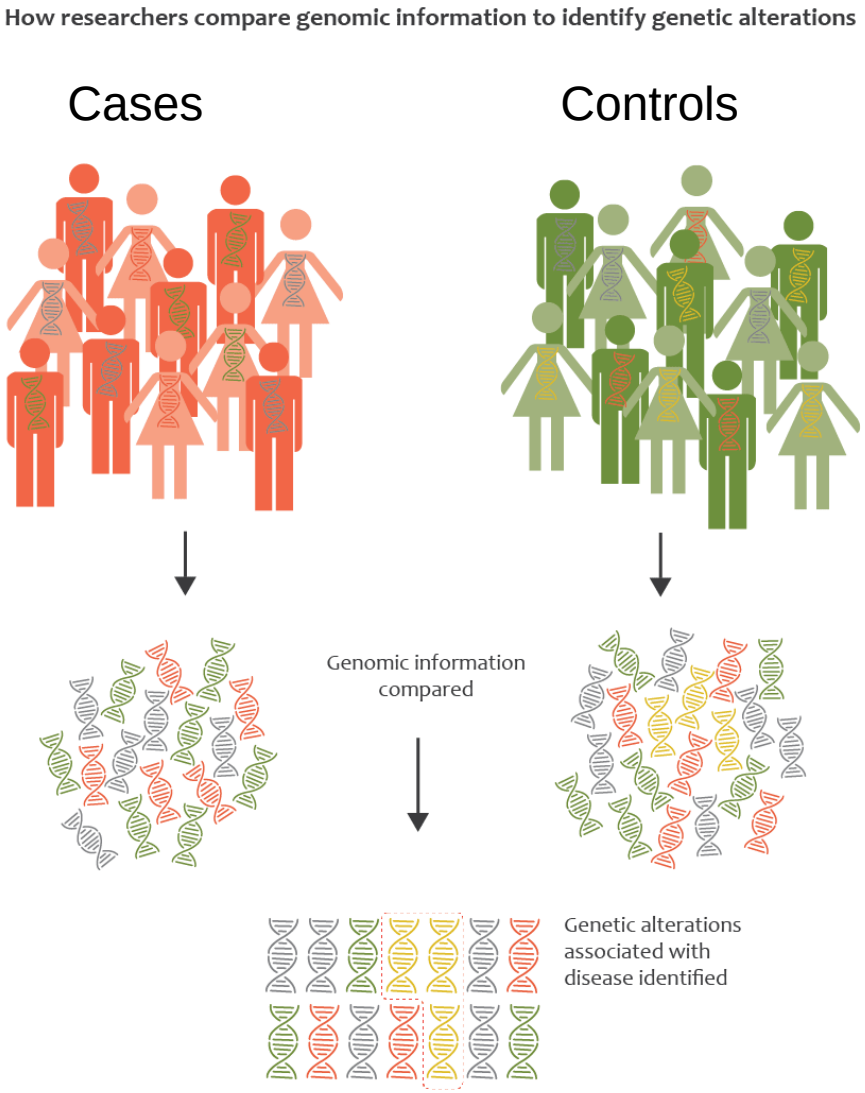
Challenges

- Highly polymorphic
- Highly correlated variants
- Study design is essential

MANCHESTER 1824
The University of Manchester

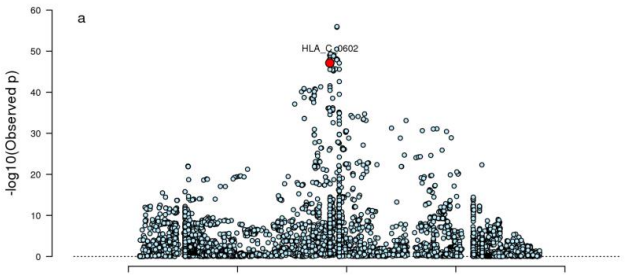
Discovery: genetic study

1. Recruitment
2. Collect genetic information
3. Compare Frequencies
4. Genetic basis for disease



MHC fine mapping

PsA



HLA-C

Forward stepwise logistic regression

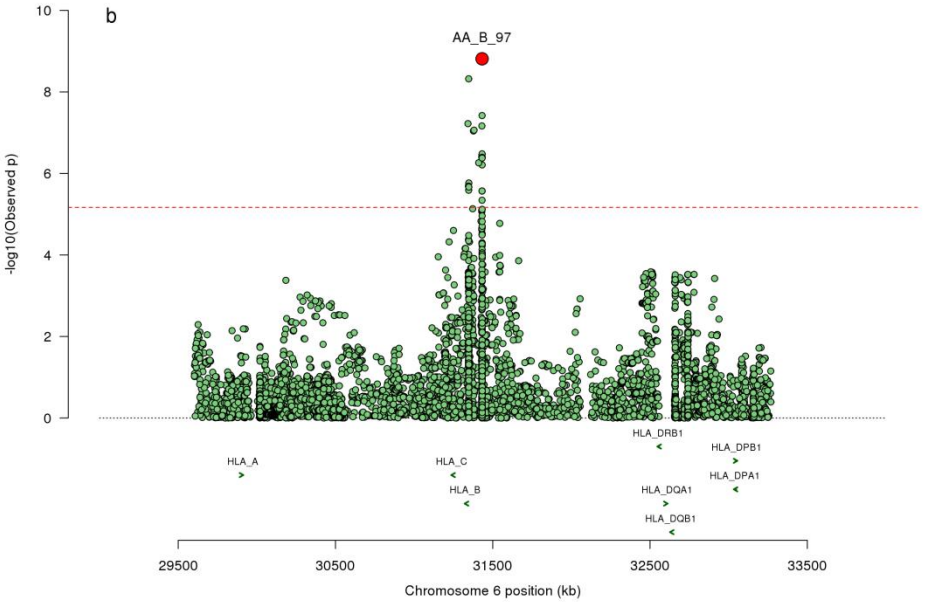
- Comparison to controls is problematic
- All our patients also have psoriasis
- Challenging to identify PsA-specific effects
- MHC – identical to PsC
- Any potential PsA signal is lost

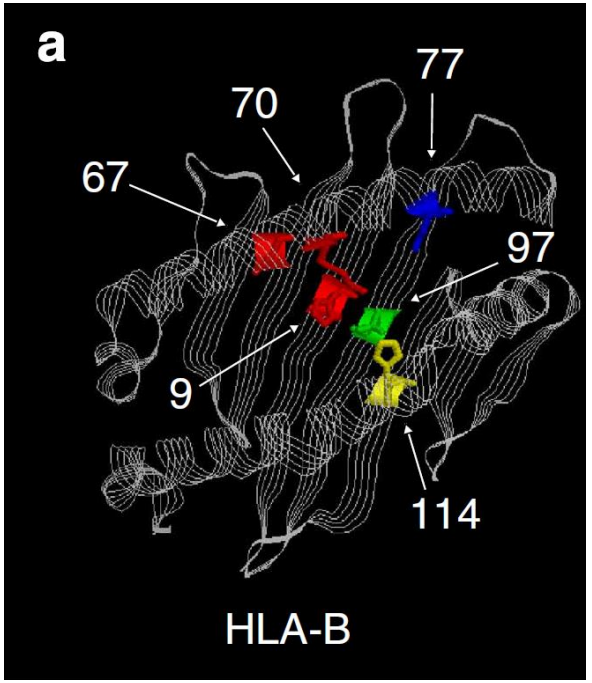
Cross-phenotype analysis

- Modified study design: integrate psoriasis genotype data
- Access to psoriasis cohort
- Collaborate King's College London
  - Catherine Smith
  - Jonathan Barker
  - Richard Warren
  - Christopher Griffiths
- Data from the BSTOP study

Biomarkers of Systemic Treatment Outcomes in Psoriasis

Cross-phenotype analysis



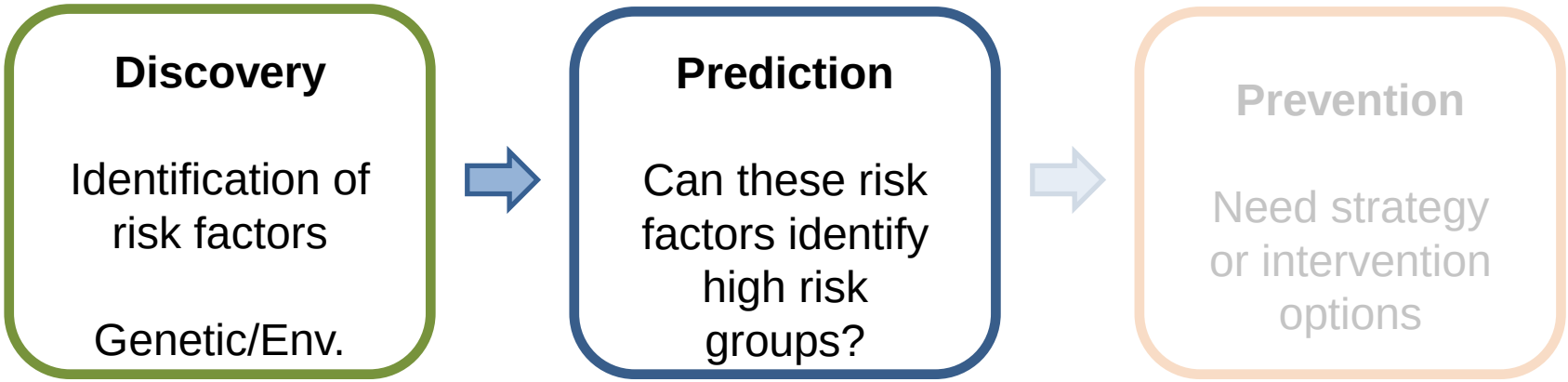


- Direct comparison
- No effect from known psoriasis risk variants
- HLA-B*27
- Antigen presentation to cytotoxic T-cells

- Resolve association to amino acid 97
- Floor of the peptide binding groove
- Alter peptide specificity

MANCHESTER 1824
The University of Manchester

Pathway to prevention



MANCHESTER 1824
The University of Manchester

Disease risk prediction

Can PsA-specific variants predict disease?

Machine learning

- Recruited post-doctoral research associate
- Building collaborations with the School of Computer science
- Work funded by Arthritis Research UK project grant

Variable selection

- Which variants are good classifiers?
- Differentiate PsA from PsC
- Method: mutual information
- Important to address confounding

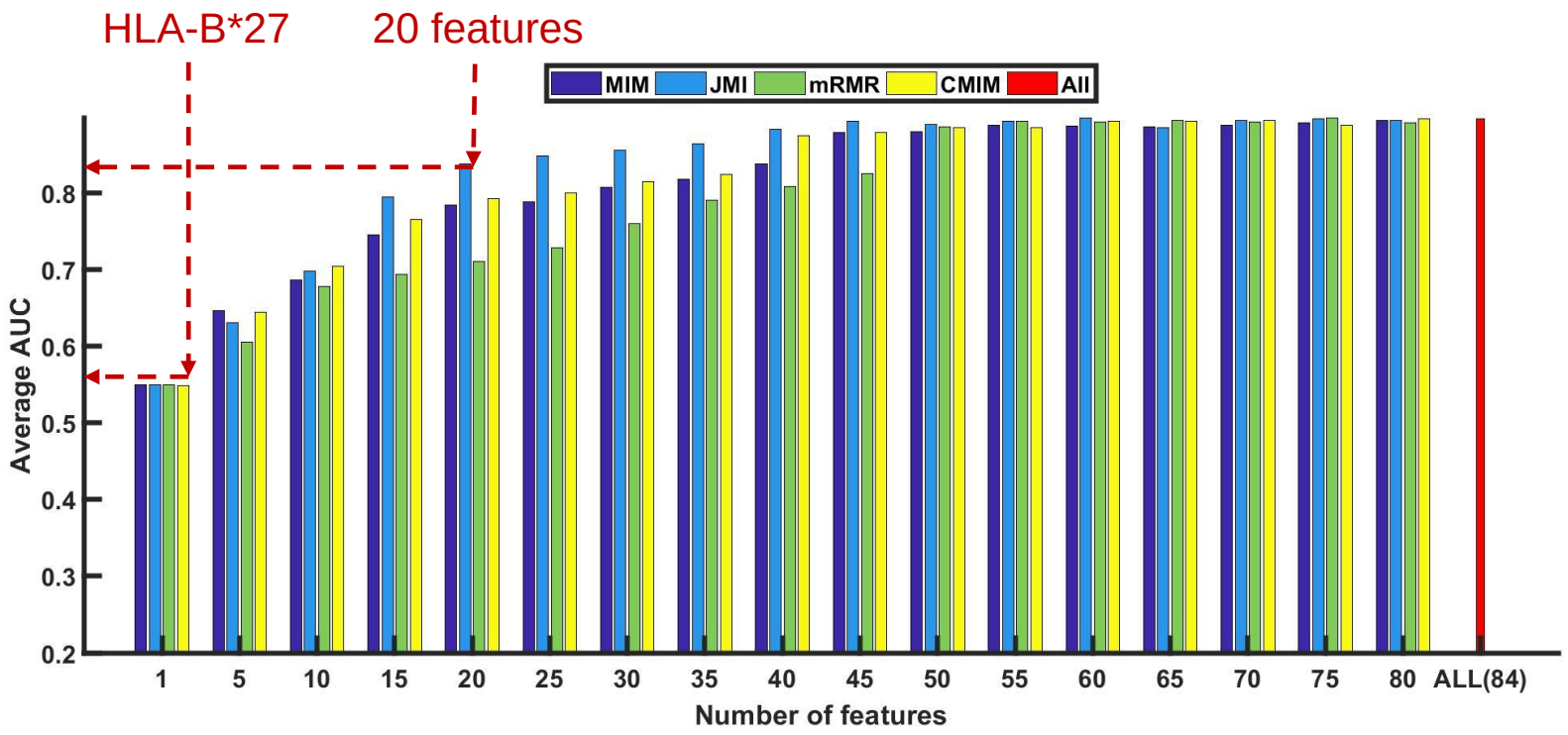
Predictive modelling

- Test the ability of variables to predict disease
- Multiple methods:
  - bagged trees
  - random forests
  - KNNC
- validate in independent data
  - UK Biobank

MANCHESTER 1824
The University of Manchester

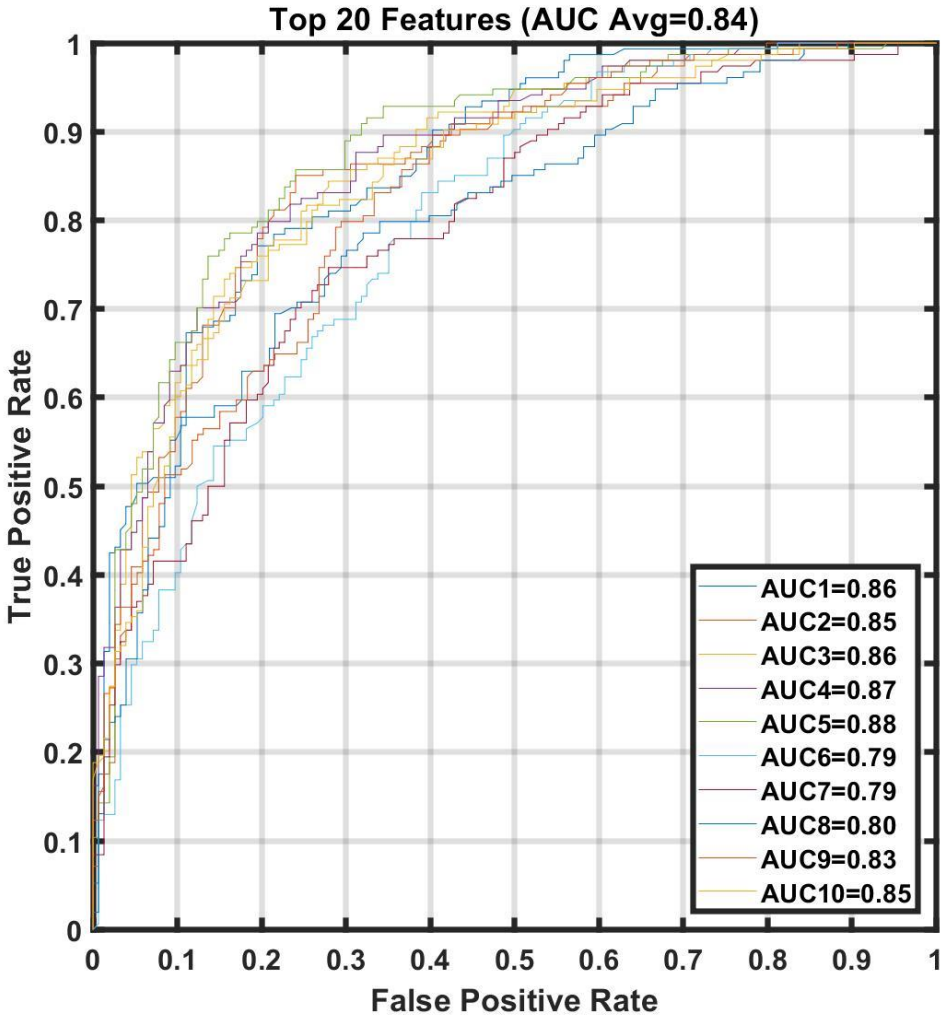
Disease risk prediction

Application to MHC data: 2 digit HLA alleles



MANCHESTER 1824
The University of Manchester

Disease risk prediction



Overfitting: Independent validation is essential

biobank uk

MANCHESTER 1824
The University of Manchester

PREVENT PsA

Genetics

Clinical

Lifestyle

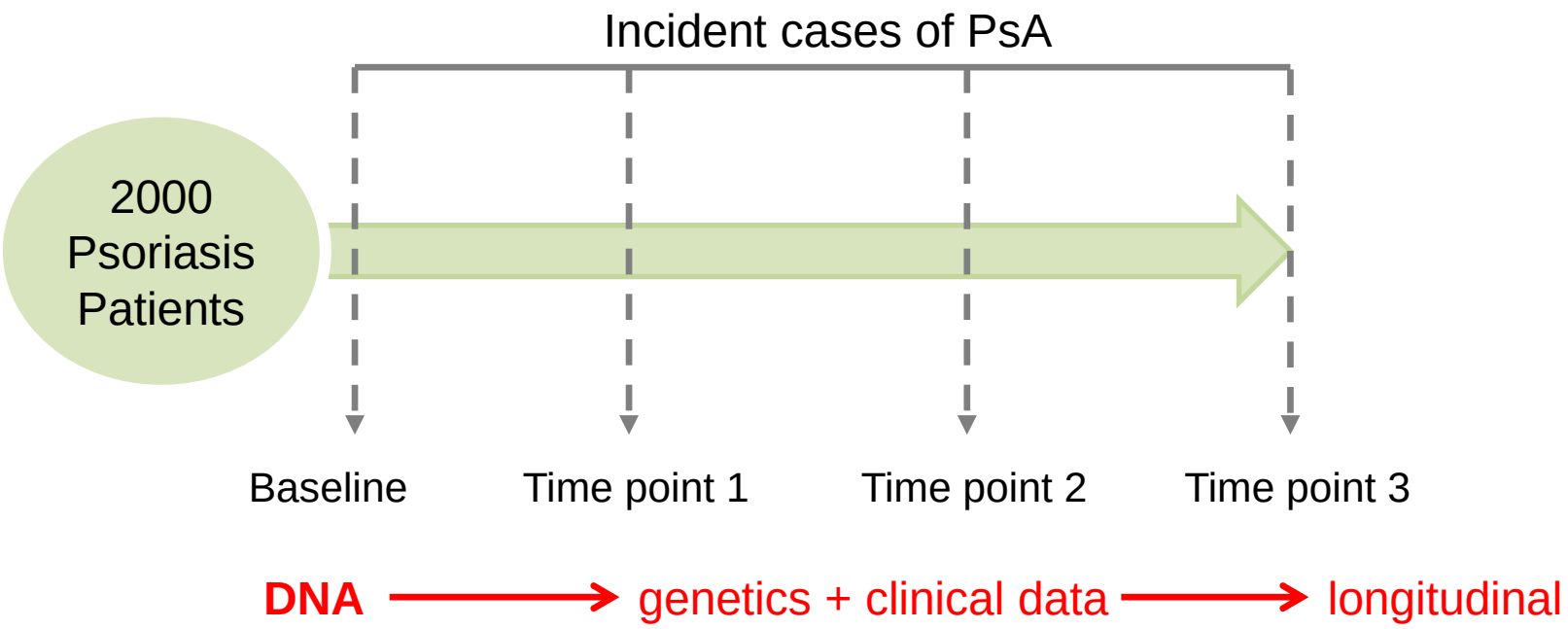
Variable selection and prediction modelling

MANCHESTER 1824
The University of Manchester

PROMPT

early detection to imPRove OutcoMe in people with undiagnosed Psoriatic arthriTis

UNIVERSITY OF BATH

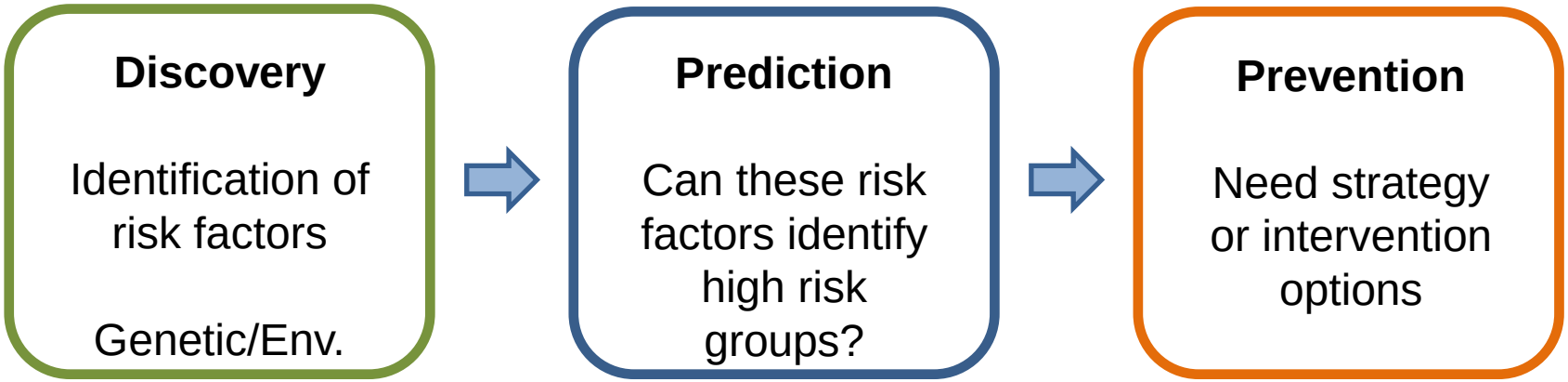


Aim: Clinical benefit of screening and early diagnosis

Extend PROMPT to include genetics

MANCHESTER 1824
The University of Manchester

Pathway to prevention



MANCHESTER 1824
The University of Manchester

Implementation

Options for preventative strategies:

1. Early referral to rheumatologist

2. Preventative treatment
- a. Statins
- b. Methotrexate
- c. Single low-dose biologic
  - Rituximab
  - Abatacept

} RA

MANCHESTER 1824
The University of Manchester

Summary

- We are identifying PsA-specific risk factors
- Showing promise in prediction models
- Moving research towards a clinical setting
- Combining genetic and clinical data

Prevention projects

Prevent PsA

- High risk groups
- Early intervention or preventative treatment
- *Prevent*: disease

Comorbidities

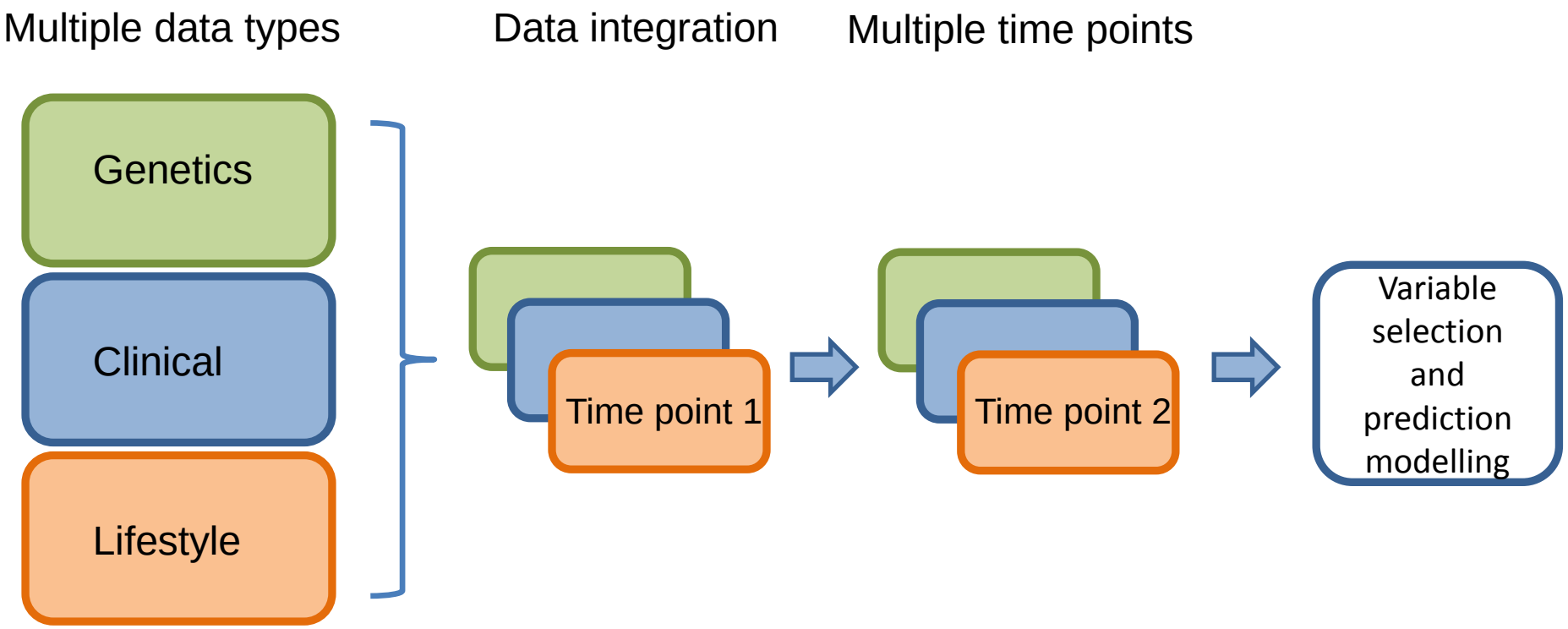
- Increased prevalence in IA
- Understand this relationship
- *Prevent*: morbidity

Uveitis JIA

- Common in JIA
- Can lead to blindness
- *Prevent*: burden of screening – reduce intervention

MANCHESTER 1824
The University of Manchester

Current work: data integration



Acknowledgements

Manchester:

Professor Anne Barton (PI)

Dr Farideh Jalali

Australia:

Prof. Matthew Brown (The University of Queensland)

Dr. Marie Feletar (Monash University)

PAGE Collaborators:

Prof. Neil McHugh (University of Bath)
Prof. Ann Morgan (University of Leeds)
Prof. Andre Reis (Erlangen University)
Prof. Oliver FitzGerald (University College Dublin)
Prof. Emiliano Giardina (University of Rome)
Dr. Philip Helliwell (Leeds University)
Dr. Gerd-Marie Alenius (University Hospital, Umea)
Prof. Harald Burkhardt (Goethe University)

MANCHESTER 1824
The University of Manchester