General considerations to develop and use biomarkers in MS
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Klinikum rechts der Isar
Technische Universität München

Neuro-Kopf-Zentrum
Neurologische Klinik und Poliklinik

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From Early Outcome Prediction to Individualized Treatment Decisions – Neurology Use Cases Utilizing Data Integration and Data Sharing

Bernhard Hemmer

Overview

- Why use case multiple sclerosis?
- From clinical care to outcome prediction in multiple sclerosis
- Other neurological use cases

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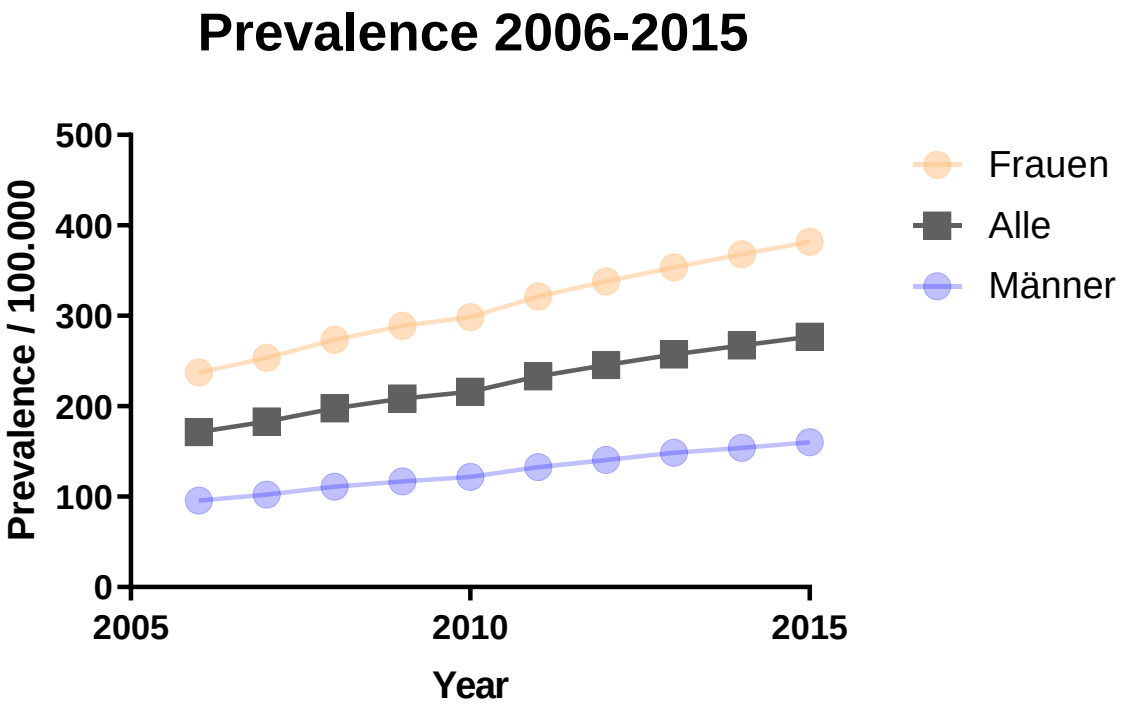
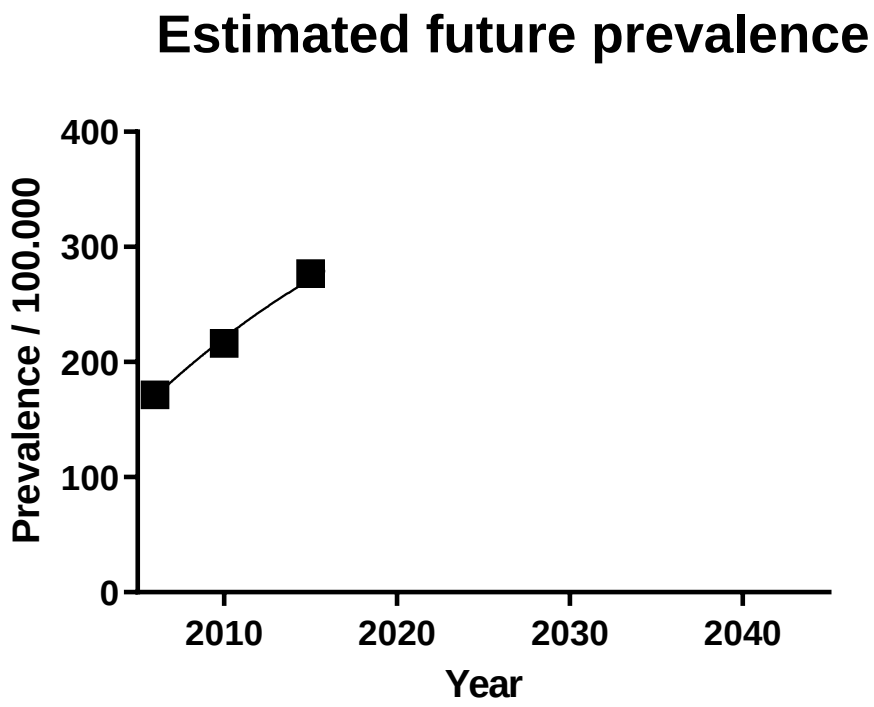
Why use case multiple sclerosis?

- Most frequent non-traumatic cause of disability in young adults
- Worldwide more than 2.5 million people affected
- Increasing prevalence

Prevalence of MS in Bavaria





Bavarian Association of Statutory Health Insurance Physicians

Daltrozzo, Front Neurol 2018

Why use case multiple sclerosis?

- Visible multiple sclerosis research at all clinical sites
- Established national and international collaborations

Kompetenznetz Multiple Sklerose

IMSGC International Multiple Sclerosis Genetics Consortium

KVB Kassenärztliche Vereinigung Bayerns

DZNE Deutsches Zentrum für Neurodegenerative Erkrankungen in der Helmholtz-Gemeinschaft

SyNerg Munich Cluster for Systems Neurology

MultipleMS

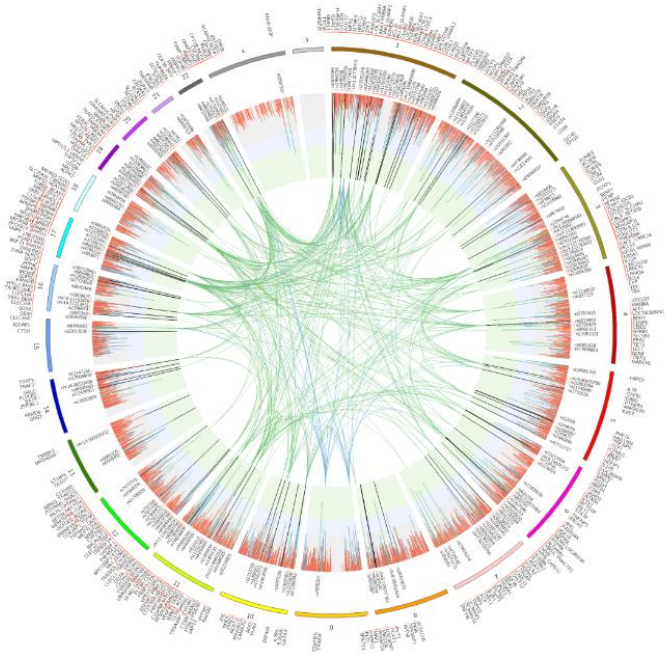
Multiple Sclerosis SFB/CRC-TR 128

ABIRISK

MS Genetics

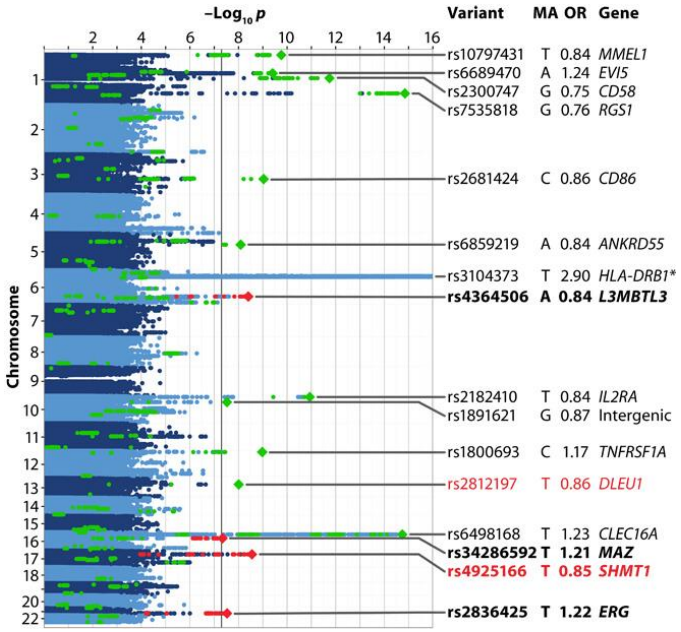
HLA Alleles

DRB1*1501, 1*1303, 1*0301 (OR 1.5-3.2)
DRA*0201 (OR 0.7)



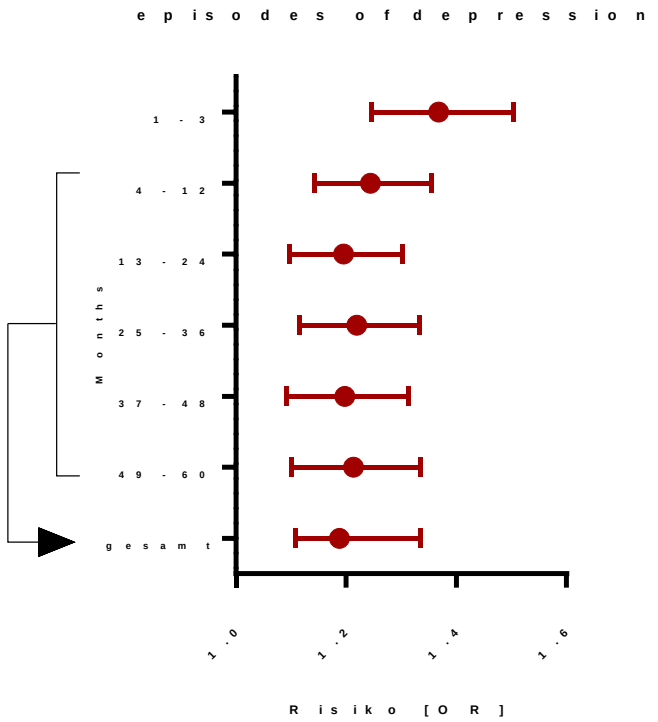
IMSGC, Nature 2011, IMSGC Nat Gen 2013, Moutsianas, Nat Gen 2015, IMSGC, Cell 2018, IMSGC, BioRxiv

>200 genetic variants (OR 1.05-1.3)



Dankowski, Genet Epidem. 2014, Andlauer, Science Adv. 2016

Prodromal phase



Depression

Anxiety Numbness

Spinal disc herniation

Dizziness

Visual impairment

Mononucleosis

Diagnosis of MS/CIS

5 – 10 years

Respiratory infection

Vaccination

Multiple Sclerosis	12,262
Healthy controls	79,185
Crohn's disease	19,296
Psoriasis	112,292

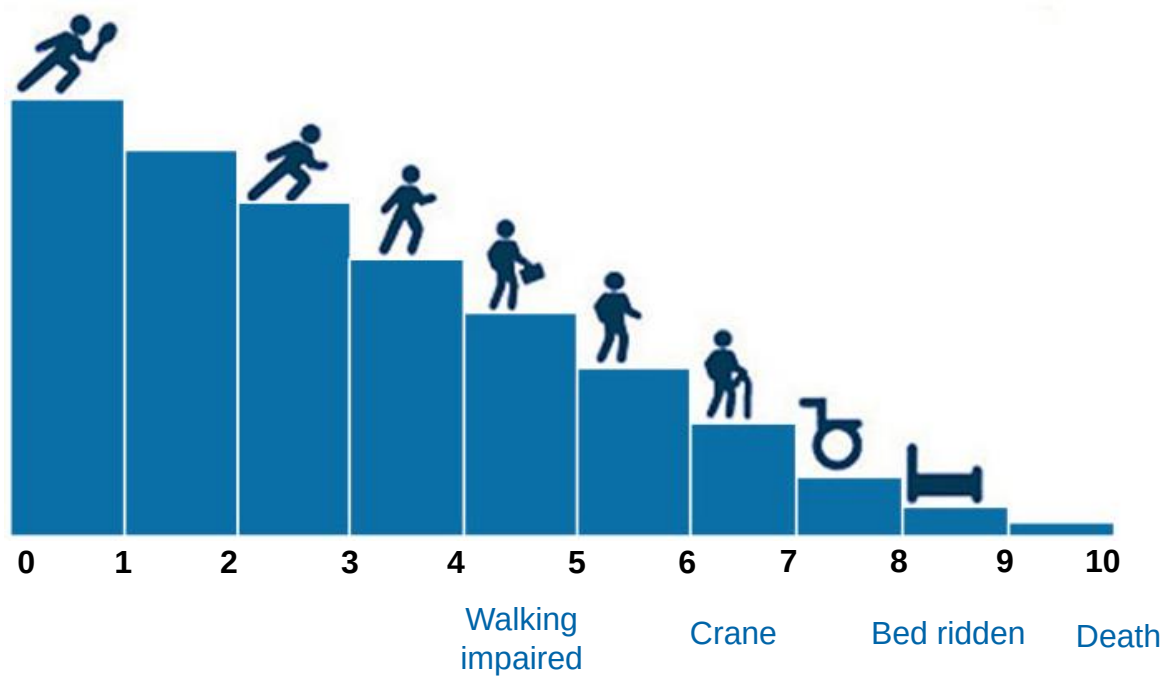
Bavarian Association of Statutory Health Insurance Physicians

Hapfelmeier, in preparation

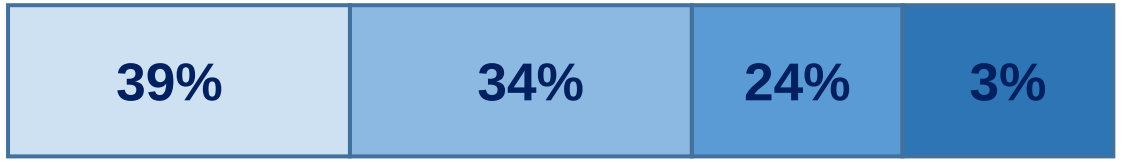
Why use case multiple sclerosis?

- MS has become a treatable diseases
- fifteen disease modifying drugs are approved for treatment of MS, which differ significantly in their mode of action, efficacy and side effect profile
- MS drugs are very expensive (yearly costs 15,000 – 33,000€)

Why use case multiple sclerosis?

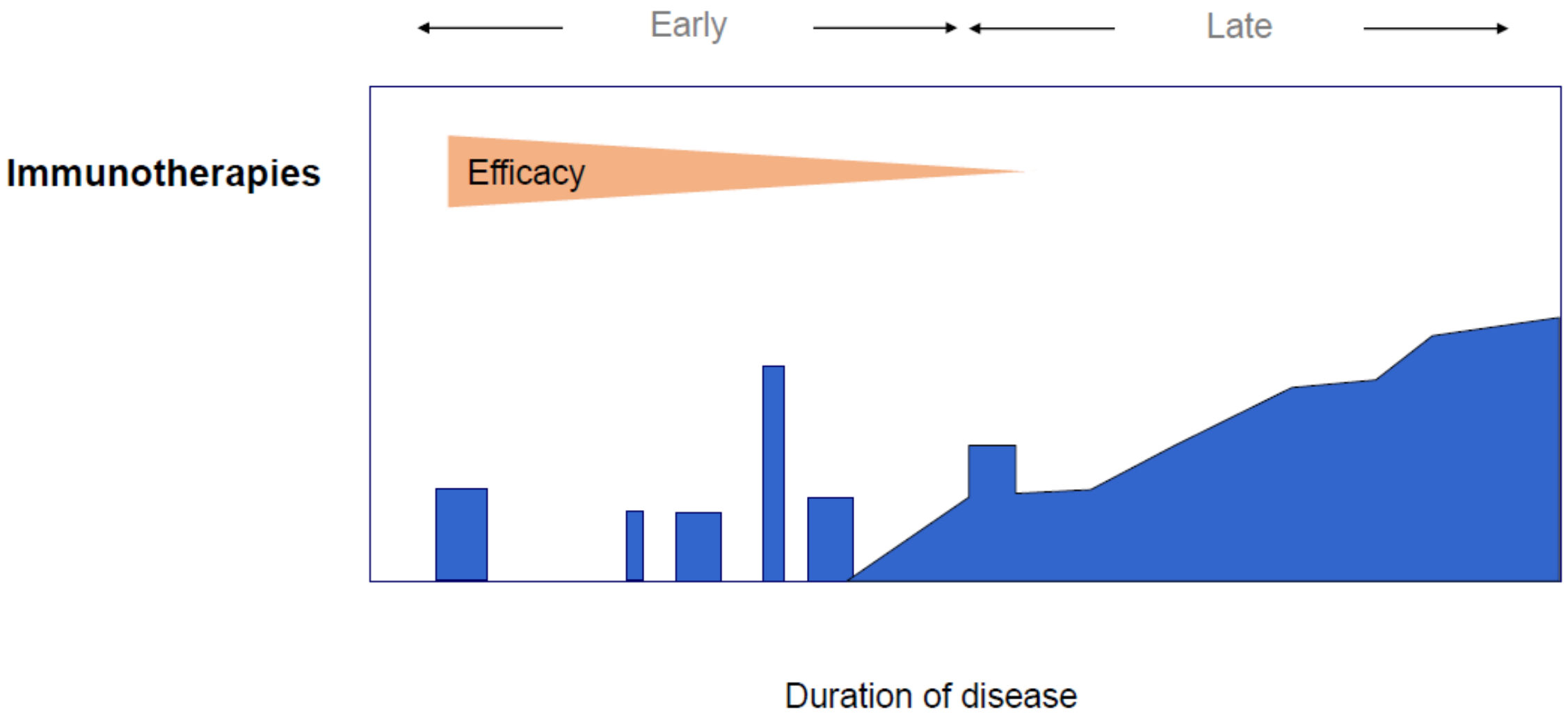


After 15 years

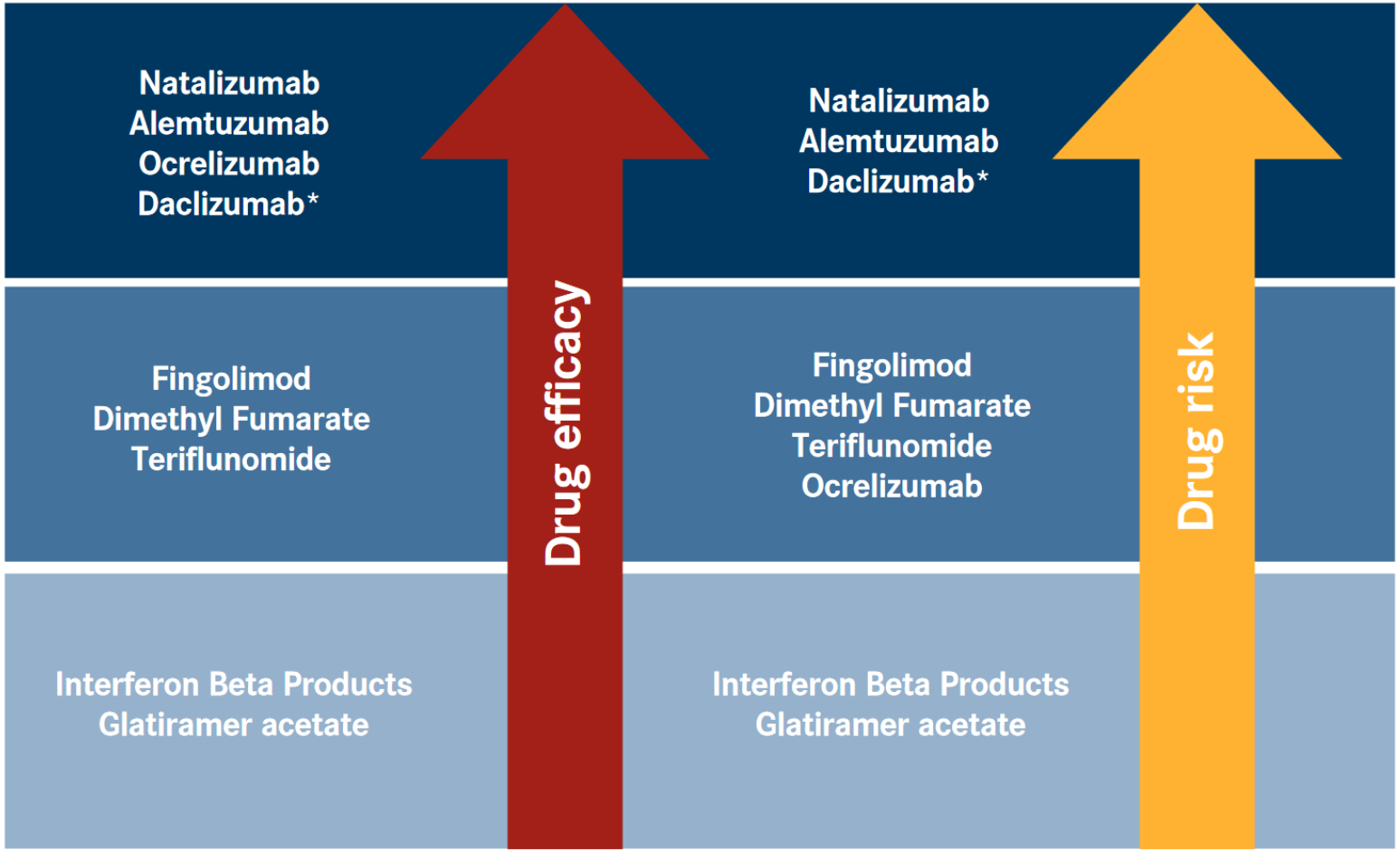


Hughes et al, JNNP 2012

Why use case multiple sclerosis?



Why use case multiple sclerosis?



FDA indicates Food and Drug Administration.
Figure reprinted with permission from EW Associates, LLC.

Why use case multiple sclerosis?

Disease modifying treatment (DMT) should be initiated as early as possible. The treatment should be selected based on the predicted course of disease, treatment response and adverse events of the treatment.

A subset of patients does not require DMT, others need the most effective DMT as early as possible.

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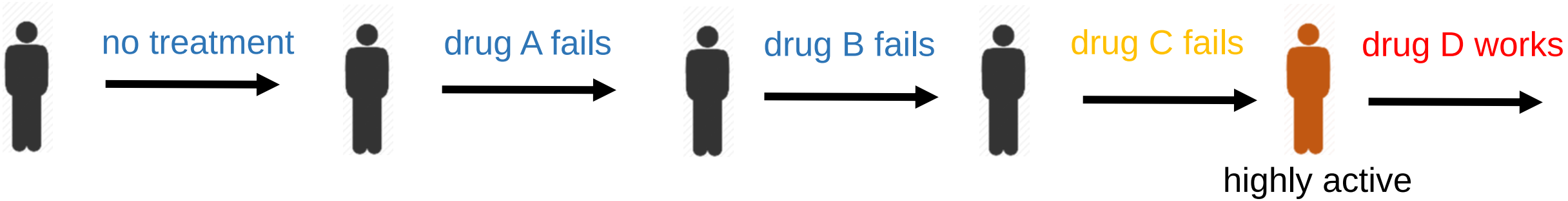
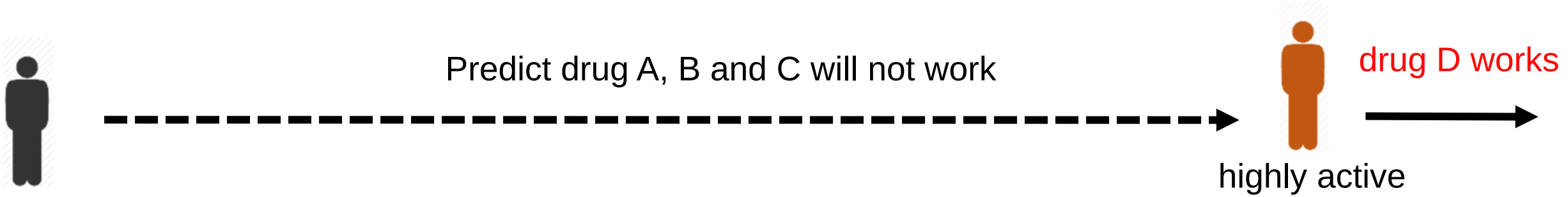
What is missing

Current strategy



Future strategy



Parameters associated with outcome

- **Clinical parameters**: age, gender, initial symptom, relapse severity, frequency of relapses, incomplete recovery from relapse
- **MRI**: number and volume of lesions at onset, distribution of lesions, development of new lesions, brain and spinal cord atrophy
- **Laboratory**: CSF parameters (IgG, OCBs), neurofilament (CSF, blood), neutralizing antibodies to biopharmaceuticals
- **Electrophysiological**: visual and sensory evoked potentials
- **Optical coherence tomography**: retinal layer atrophy
- **Genetics**: HLA, susceptibly alleles
- **Comorbidity**: obesity, psychiatric diseases, smoking, vitamin D deficiency

Retrospective data analysis

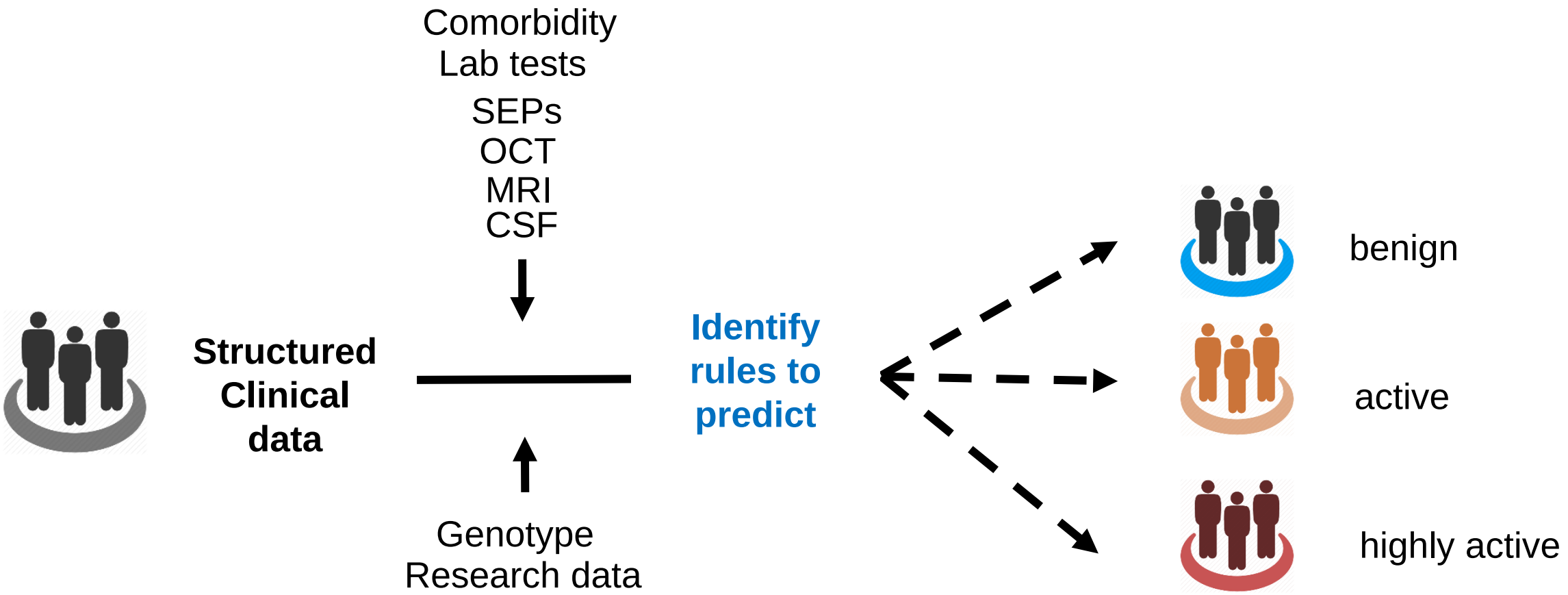
Data from more than 5,000 MS patients in University centers

- since 2010 structured clinical documentation, standardized cerebral and spinal MRI, optical coherence tomography imaging, genotypes, laboratory and electrophysiological data
- harmonized between centers in 2017

Data from more than 30,000 MS patients in the database of the Bavarian Association of Statutory Health Insurance Physicians

- all diagnoses and procedures performed in the outpatient setting (before and after diagnosis)

Retrospective data analysis



Prospective multi site study

Newly diagnosed MS patients

Technische Universität München · LMU Ludwig-Maximilians-Universität München · Eberhard Karls Universität Tübingen · Universität Augsburg University

Treatment successful?
Correct decision by treating physician?

Observation

Integrated data

New rules identified

Prediction

prospective study to evaluate and validate (multidimensional) rules to predict individual outcome 24 months after diagnosis of multiple sclerosis

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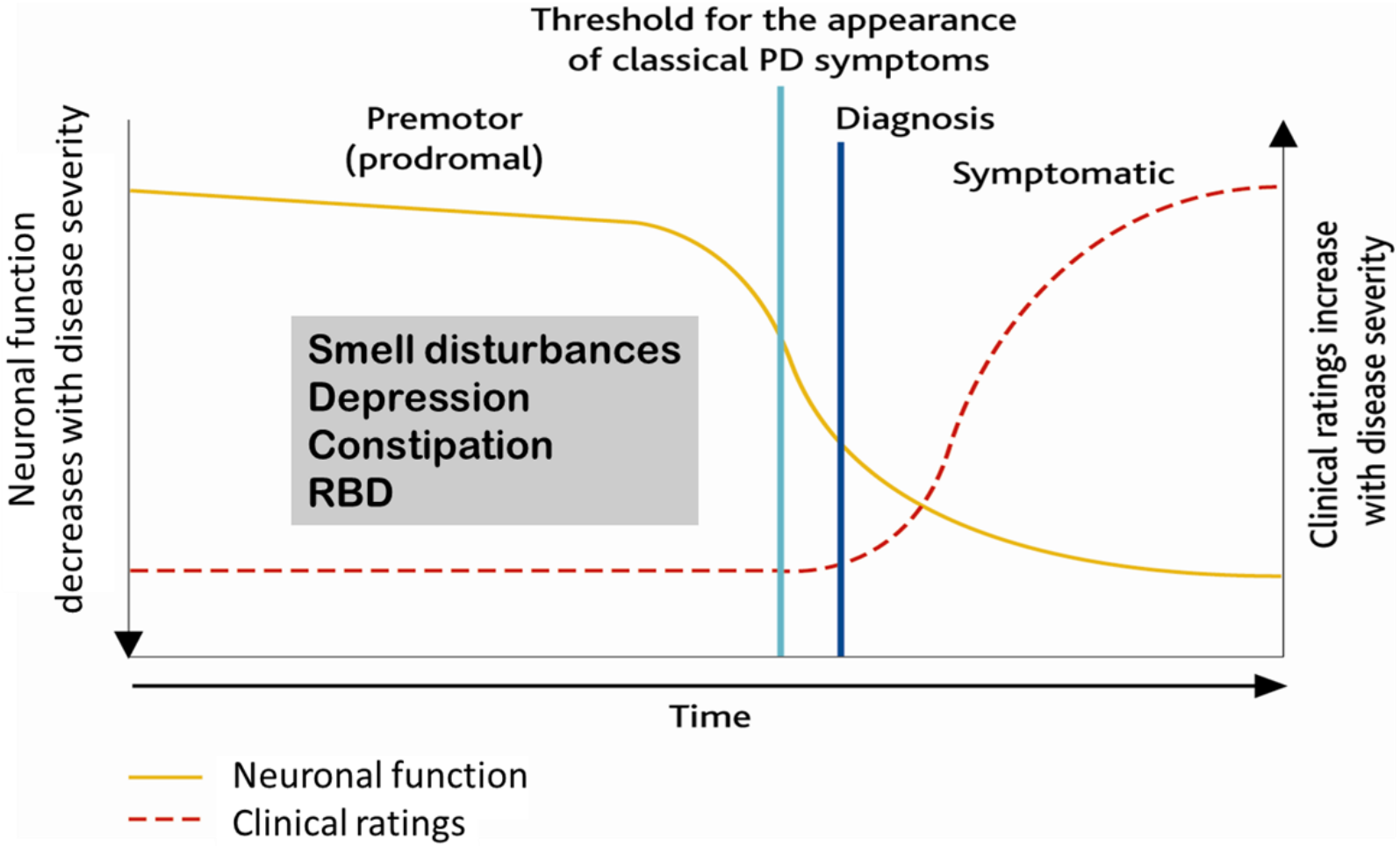
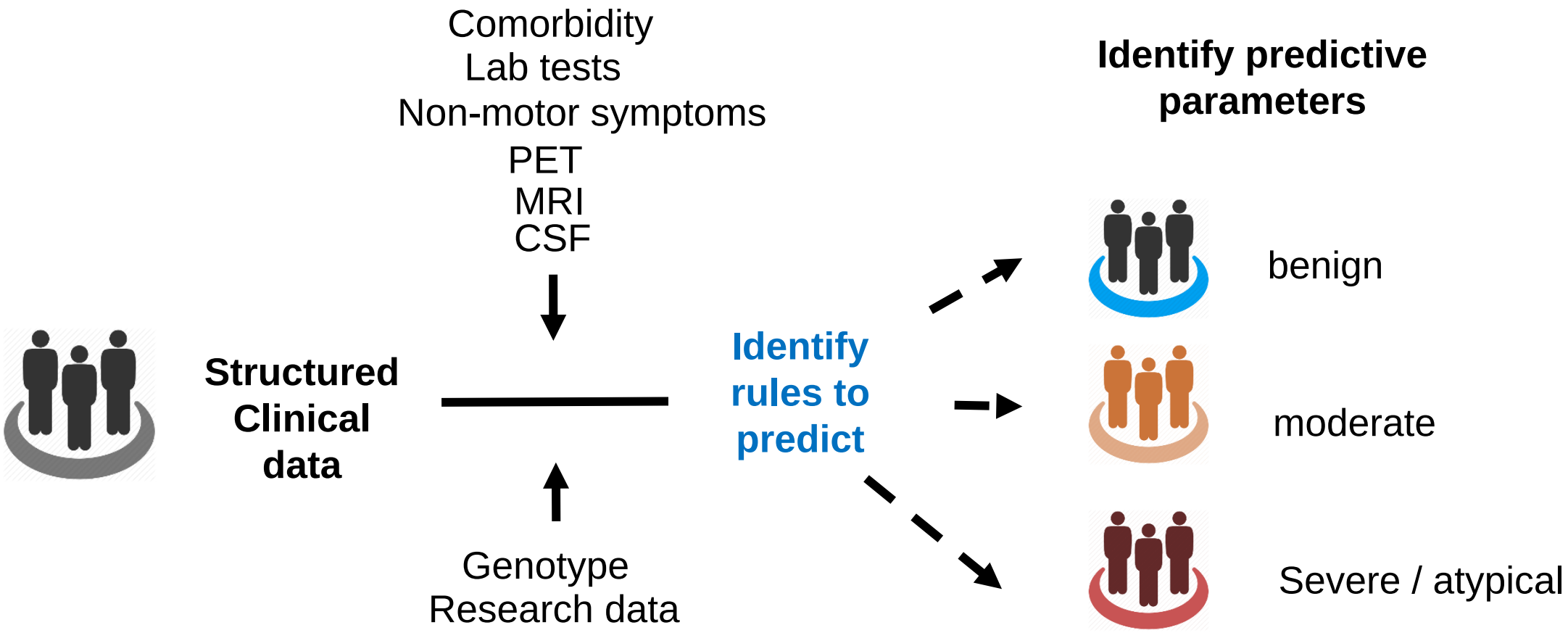
Parkinson Syndrome



Adapted from DeKosky & Marek. Science 2003; 302 (5646): 830

Retrospecitve data analysis in Parkinson diseases



Summary

- Multiple sclerosis is a prototypic disease for personalized treatment decisions
- The development and implementation of predictive rules for newly diagnosed patients will have a major impact on patient care
- The MS use case will also provide a rich source for clinical and basic research
- The MS use case will serve as a blueprint for other diseases

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