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

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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

Prevalence 2006-2015

Estimated future prevalence

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

>200 genetic variants (OR 1.05-1.3)

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

Dankowski, Genet Epidem. 2014,
Prodromal phase

Diagnosis of MS/CIS

- Depression
- Anxiety
- Numbness
- Spinal disc herniation
- Dizziness
- Visual impairment
- Mononucleosis

5 – 10 years

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

Episodes of depression

Risk [OR]

Respiratory infection

Vaccination

Bavarian Association of Statutory Health Insurance Physicians

Hapfelmeier, in preparation
Why use case multiple sclerosis?

- MS has become a treatable disease.
- 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

- Walking impaired: 39%
- Crane: 34%
- Bed ridden: 24%
- Death: 3%

Hughes et al, JNNP 2012
Why use case multiple sclerosis?
Why use case multiple sclerosis?

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

no treatment → drug A fails → drug B fails → drug C fails → drug D works

Future strategy

Predict drug A, B and C will not work → drug D works

highly active
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, susceptibility 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

Structured Clinical data

Comorbidity Lab tests
SEPs OCT MRI CSF

Genotype Research data

Identify rules to predict

benign
active
highly active
Prospective multi site study

Newly diagnosed MS patients

Observation

Integrated data

New rules identified

Prediction

Treatment successful?
Correct decision by treating physician?

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

Threshold for the appearance of classical PD symptoms

Premotor (prodromal)

Diagnosis

Symptomatic

Neuronal function decreases with disease severity

Smell disturbances
Depression
Constipation
RBD

Clinical ratings increase with disease severity

Adapted from DeKosky & Marek. Science 2003; 302 (5646): 830
Retrospective data analysis in Parkinson diseases

Structured Clinical data

Comorbidity
Lab tests
Non-motor symptoms
PET
MRI
CSF

Genotype
Research data

Identify rules to predict

Identify predictive parameters

benign
moderate
Severe / atypical
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