HMNC Brain Health

ABCB1-Test

Optimizing pharmacotherapy of depression through genotyping

Paris, June 20, 2018

Antidepressant treatment: Current situation and how to improve

- All currently used antidepressants are unspecific pharmacologic modifications of drugs that have been on the market for **over 60 years**
- Less than **1/3** of depressed patients experience a **complete remission** of their illness when initially treated for up to six weeks with antidepressant medications (Hall-Flavin et al., 2012)
- After several treatment trials only about **2/3** of depressed patients experience remission
- These drugs **help too few** people, it **takes too long** until they work, and they have **too many side effects**

How can we improve the situation?

Personalization based on laboratory diagnostics

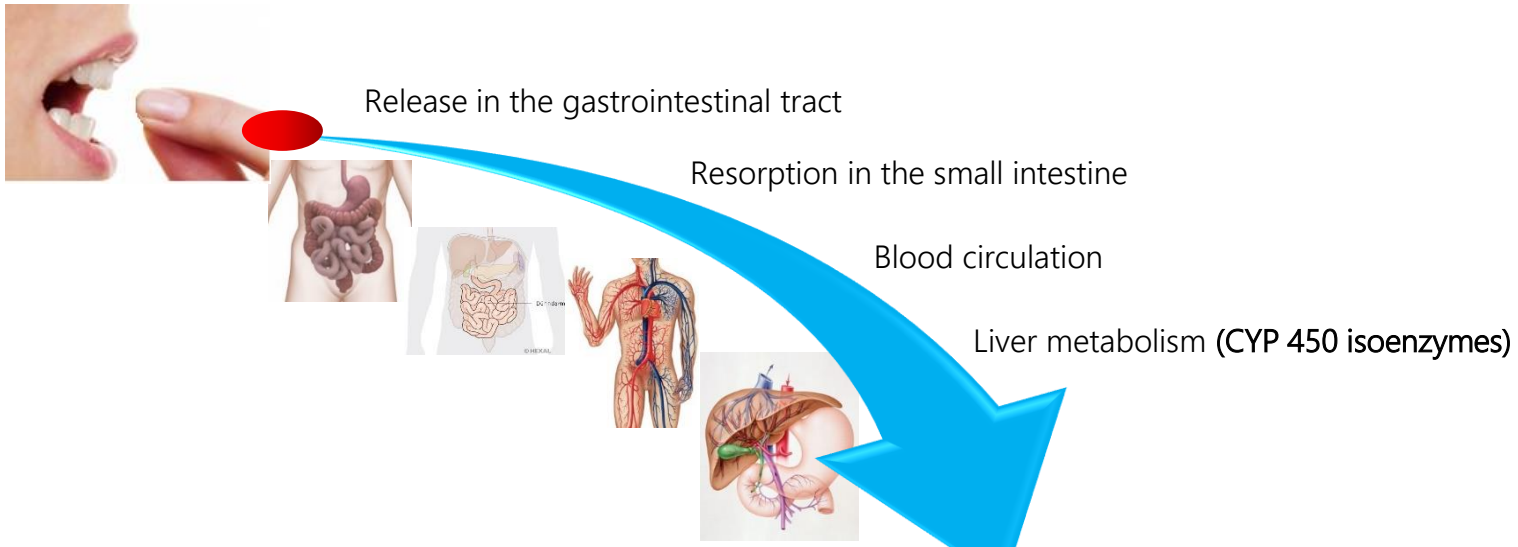
Specifically acting drugs for patients with a specific causal mechanism

stratifying populations with companion tests

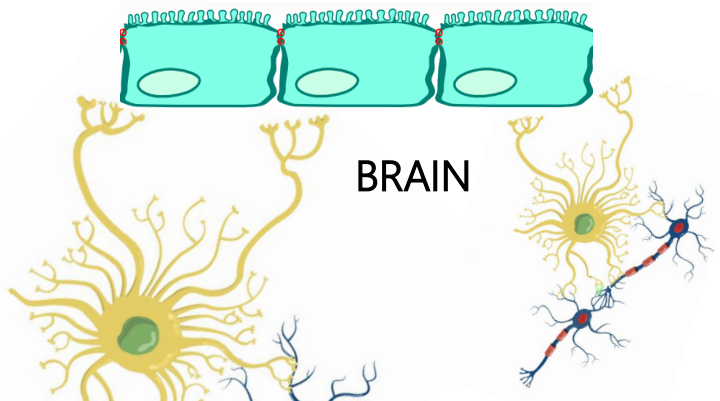
Identifying which of the current antidepressants fit best your patients genotype

pharmacokinetic testing enables precise drug selection

An antidepressants long jorney to the target site



Blood brain barrier (ABCB1)



Currently available pharmacogenetic tests to optimize depression therapy

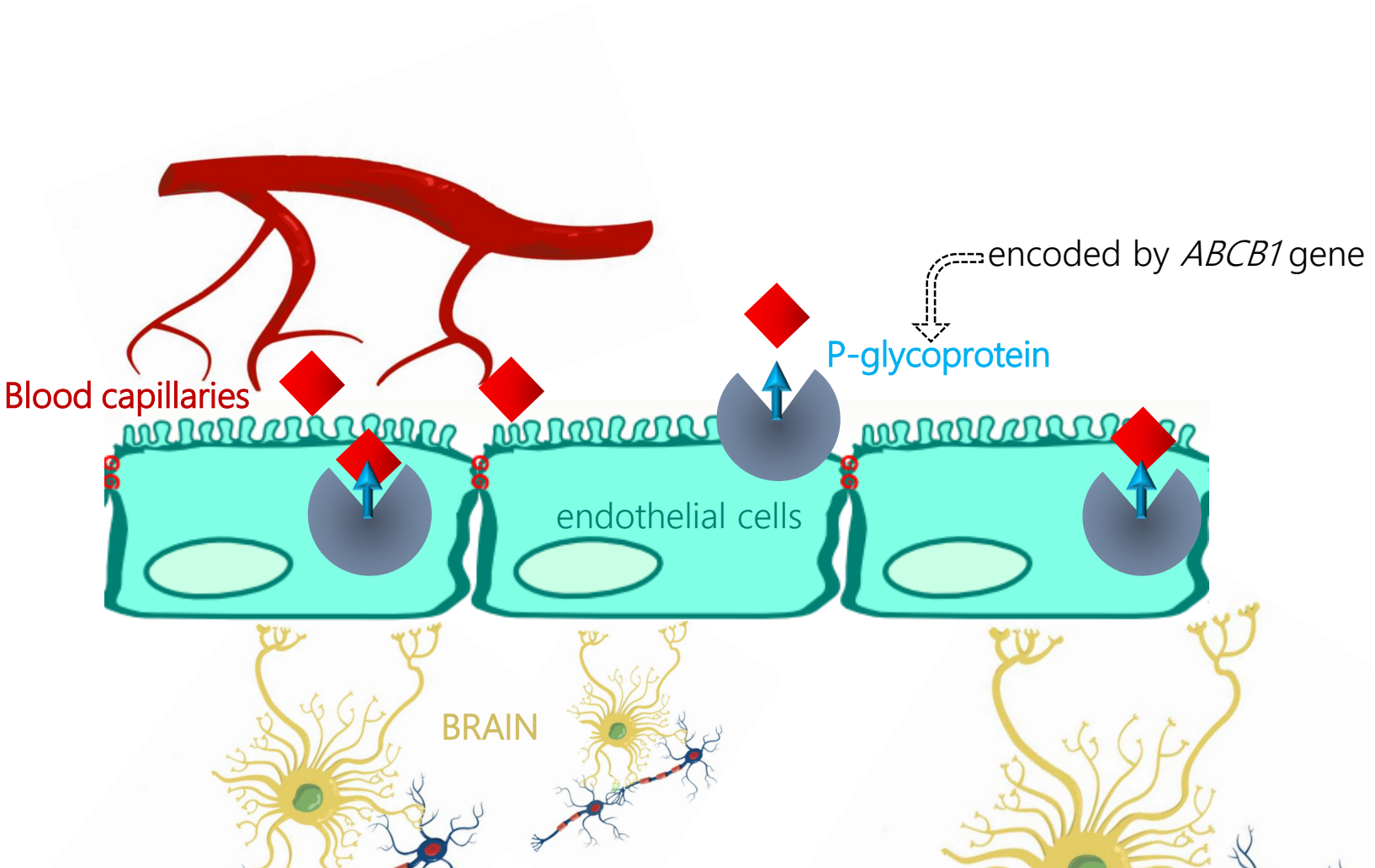
PHARMACOGENETIC GENE TESTS ON THE MARKET

CYP 450* CYP 2D6; CYP 2C19	Stada
ABCB1* rs2032583; rs2235015	HMNC
Multiplex gene test** CYP 2D6; CYP 2C19; CYP 1A2; SLC 6A4; HTR 2A	AssureRx Health / Myriad

* pharmacokinetic
** pharmacokinetic and pharmacodynamic

HMNC

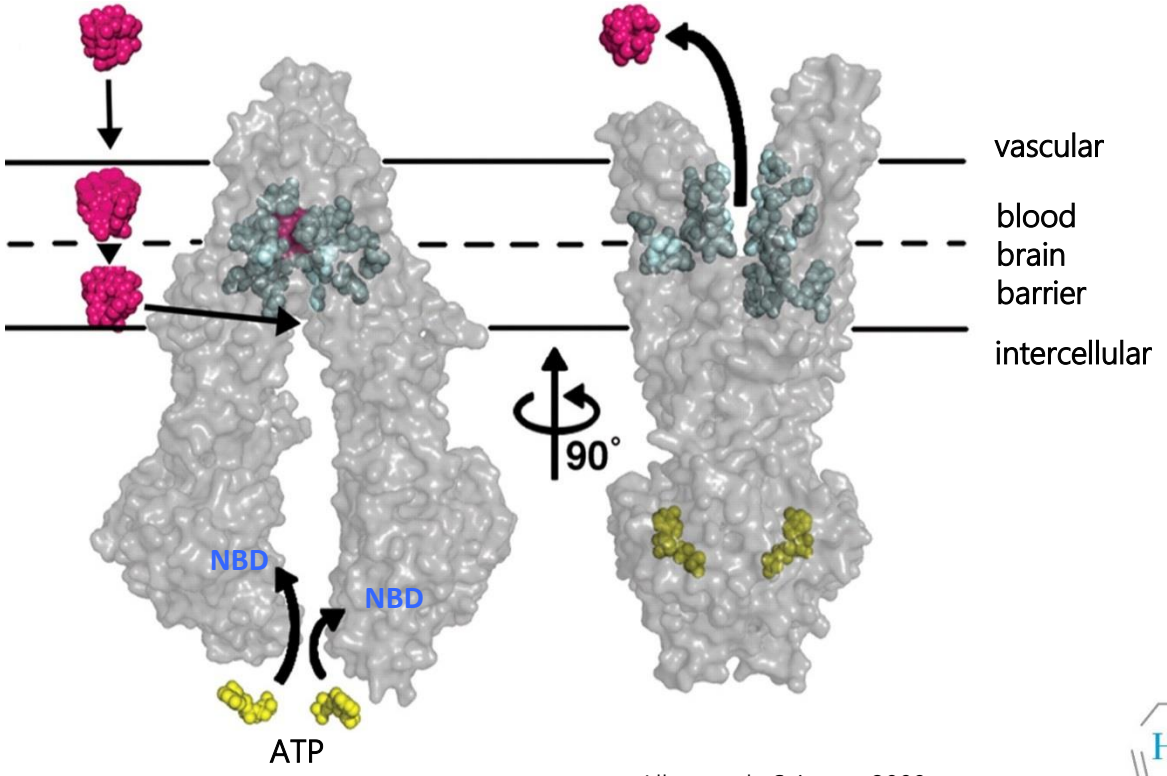
The blood brain barrier and the role of P-glycoprotein („custodian molecule")



The ABCB1 gene encodes a „custodian molecule“ that determines drug penetrance into the brain

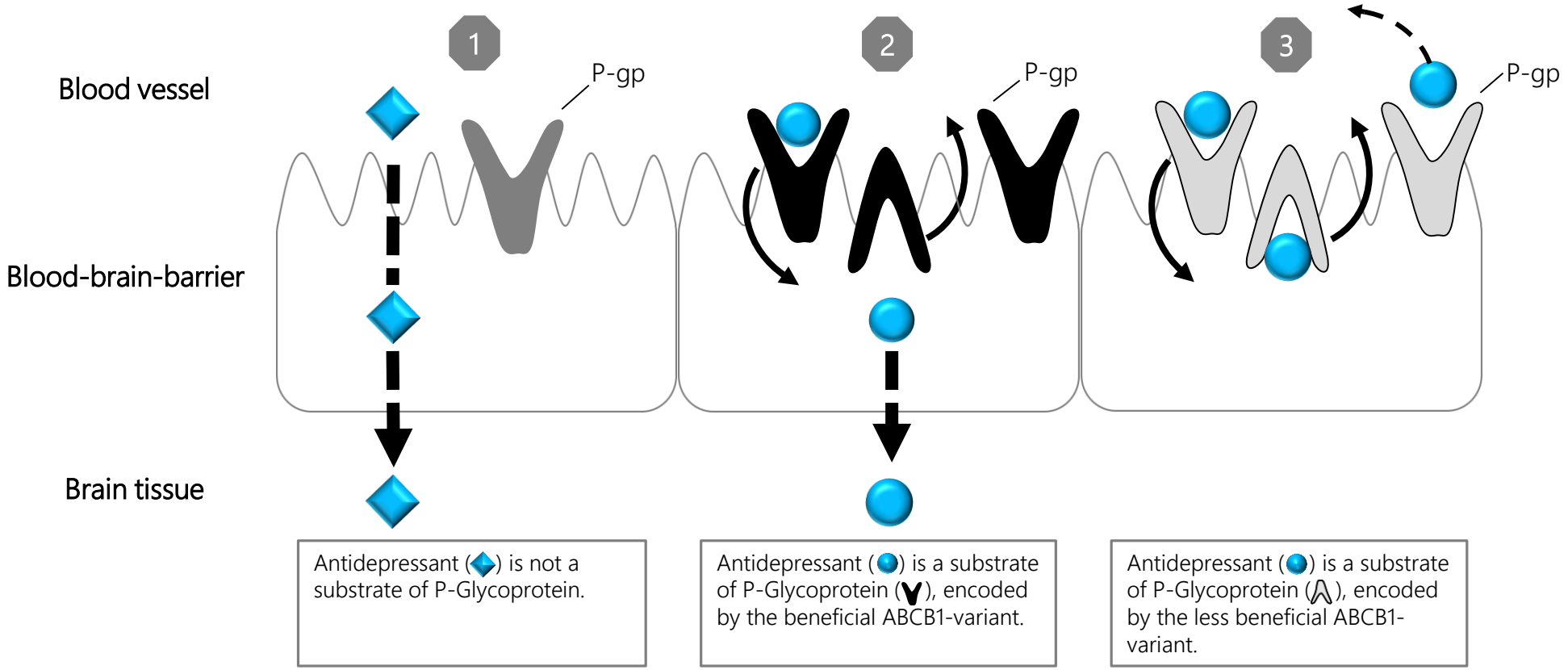
- ATP-cassette subfamily member that encodes P-glycoprotein expressed in the epithelial cells of the intestine and the endothelial cells of the blood-brain barrier
- Intestinal P-glycoprotein actively transports drugs from the cell membrane back into the intestine preventing that the drug enters the blood circulation
- Blood-brain barrier P-glycoprotein prevents penetration of drugs into the central nervous system

Structure of P-glycoprotein reveals a molecular basis for polyspecific drug binding

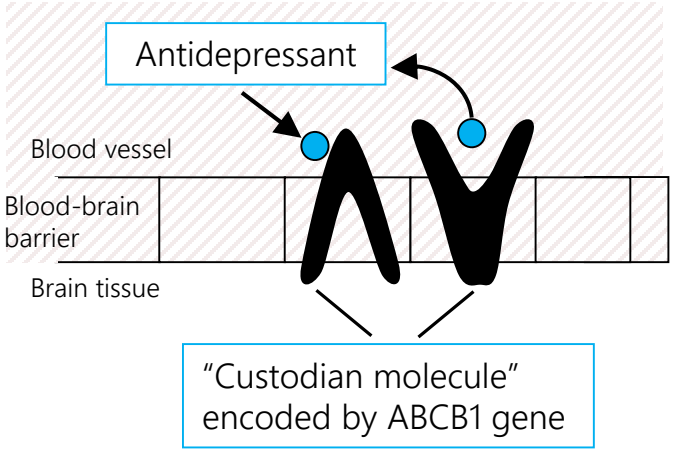


Allen et al., Science, 2009

Schematic depiction of P-gp function depending on ABCB1-genotype and substrate property of antidepressants



ABCB1 gene variants enable optimization of antidepressant drug treatment

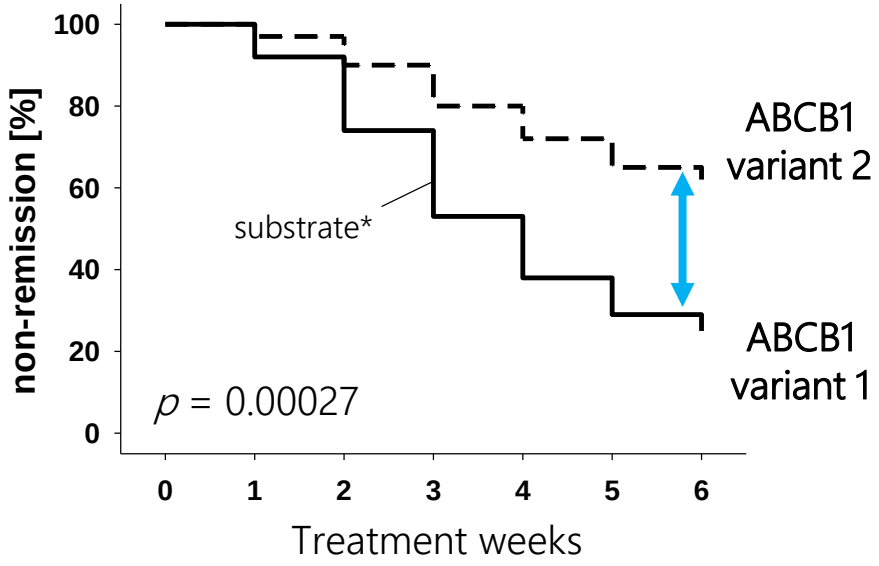


- The gene product of the ABCB1 gene, the **P-glycoprotein** (P-gp), is a custodian molecule located in the blood-brain barrier
- P-gp is a transporter that limits the passage to the brain of **many (75%) antidepressants**

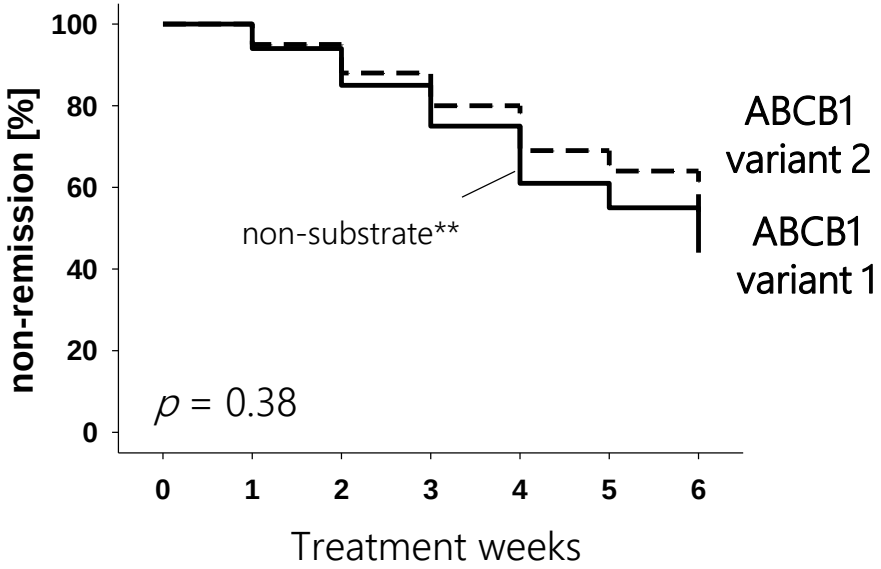
- DNA sequence variants in the ABCB1 gene **can improve prediction of individual treatment response** to antidepressants
- These sequence variants can be detected through the **ABCB1 gene test**
- The ABCB1 test **informs the physician** about adequacy of antidepressant drug and dosing

More patients achieve remission in shorter time with ABCB1 test guided therapy

TREATMENT WITH P-GP SUBSTRATES



TREATMENT WITH P-GP NON-SUBSTRATES



If patients with ABCB1 gene variant 1 are treated with antidepressant P-gp substrates and plasma level monitoring **more patients achieve remission in shorter time** (Uhr et al., 2008)

* e.g. cipralex, paroxetine

** e.g. mirtazapine, agomelatine

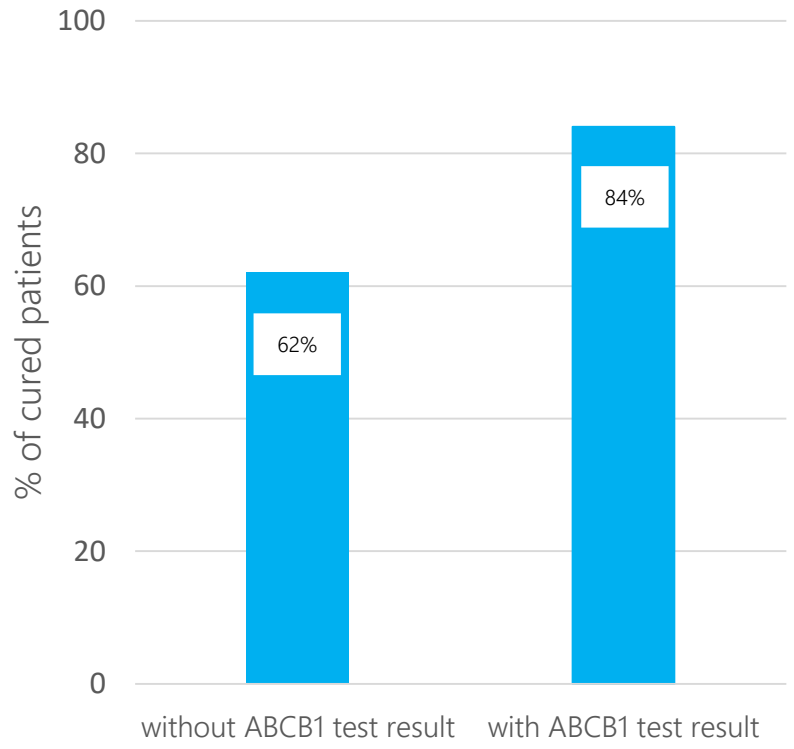
ABCB1 guided antidepressant treatment moves away from, “one size fits all” approach towards individualized medication regimes

MAJOR BENEFITS OF TESTED PATIENTS

Antidepressant drug therapy guided by ABCB1 test leads to:

- a **better prediction** of treatment success and occurrence of undesired side effects (Ray et al., 2015)
- **higher remission rates** (Breitenstein et al., 2014)
- and **faster** time until remission (Uhr et al., 2008)

REMISSION RATES OF TESTED VS. UNTESTED PATIENTS

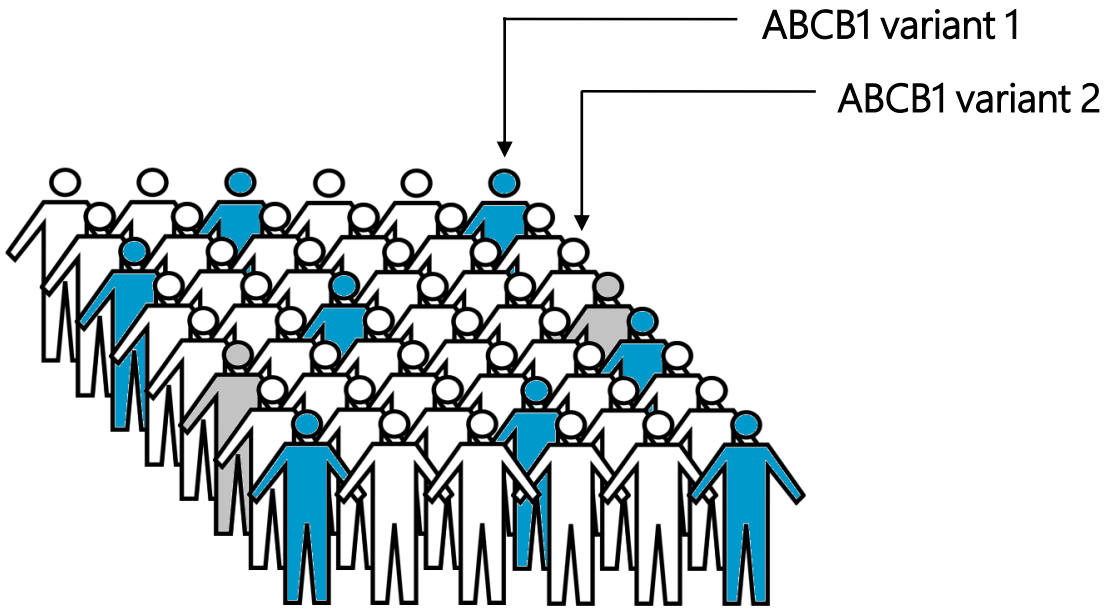


Source: Breitenstein et al., 2014

ABCB1-genotyping allows physicians a personalized antidepressant therapy

MAJOR BENEFITS OF TEST APPLICATION

- ABCB1 testing allows **individualized treatment** based on latest **scientific breakthroughs**
- Patients treated under ABCB1 guidance have **higher remission rates** (Breitenstein et al., 2014)
- ABCB1 testing allows **prediction of side effect** occurrence (Ray et al., 2015) and thus better patient **compliance**
- A **meta-analysis** comprising 2695 patients from 16 studies confirms association of beneficial response and C-allele carriers p = 0.035.
  Among inpatients (n = 485) rs 2032583 predicted beneficial outcome if treated with P-gp substrate ($p = 1.5x10^{-5}$; withstanding Bonferroni correction)



Non-remission is a strong predictor for MDD recurrency – ABCB1 testing reduces health care expenses through increased remission rates

DEPRESSION RECURRENCY IN NON-REMITTED PATIENTS

- Patients who require **more treatment steps** have **higher relapse rates** (Rush et al., 2006)
- **Non-remission** of MD episode increases risk of **future recurrency** (Judd et al., 1998)
- **Non-remission** is a strong predictor of subsequent **early relapse** (Paykel et al., 1995)

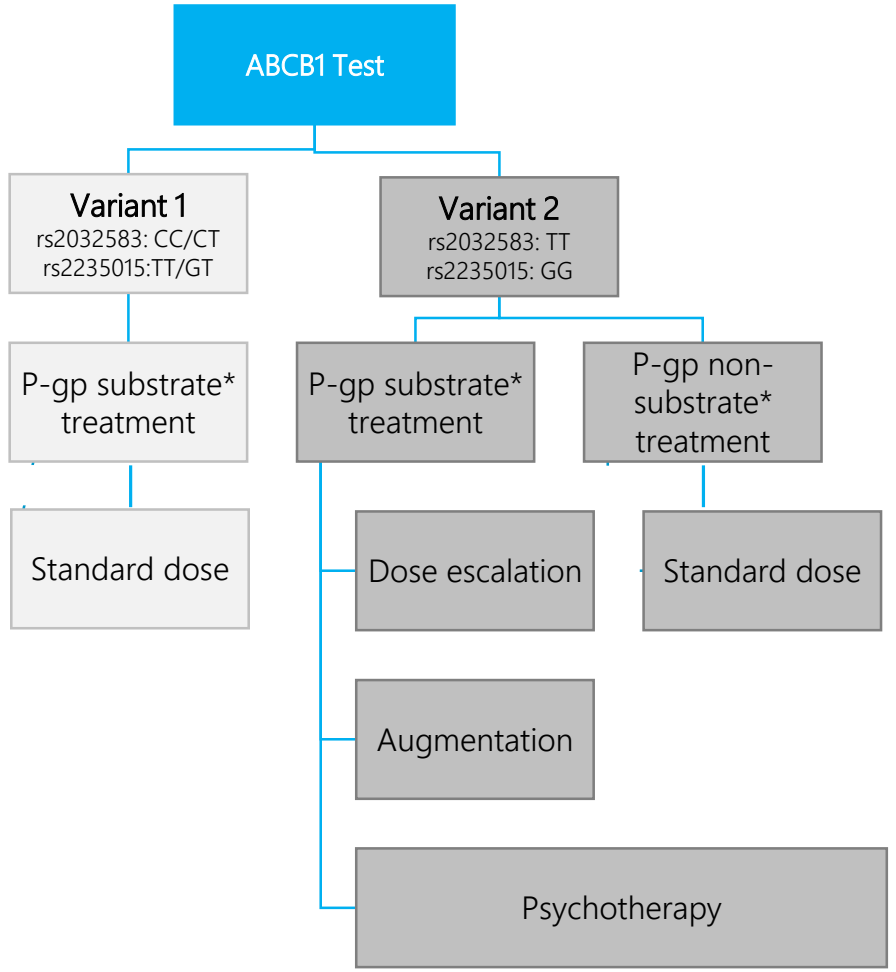
- The risk of relapse is reduced by obtaining **higher remission rates** among **ABCB1 tested** patients that were treated according to recommendations (Breitenstein et al., 2014)
- **Faster time until remission** for ABCB1 variant 1 (Uhr et al., 2008) helps to reduce treatment costs and lower sick leave costs in current depressive episode
- Payers benefit from **shorter periods of disablement and less illness episodes**

HMNC

ABCB1 Genotyping enables patient stratification and offers differential treatment algorithm

ABCB1 GENOTYPING

- Patient stratification is based on **individual pharmacogenetic patient profiles**
- The individual test result is accompanied by a specification of type and dose of **recommended antidepressant** drug
- In rare cases (5-8%) there is an unclear result and prioritizing SNP 2032583 is recommended



Most of the commonly prescribed antidepressants are P-gp substrates

ANTIDEPRESSANTS THAT ARE P-GP SUBSTRATES*

- Paroxetine
- Citalopram
- Escitalopram
- Venlafaxine
- Amitriptyline
- Amitriptyline N-oxide
- Nortriptyline
- Trimipramine
- Sertraline
- Levomilnacipran
- Vilazodone
- Doxepine
- Vortioxetine
- Duloxetine (weak)
- Hypericum

EXAMPLES FOR NON-SUBSTRATES:

- Fluoxetine
- Mirtazapine
- Agomelatine
- Bupropione
- Lamotrigin

* A P-gp substrate is a drug that is recognized by the P-gp transporter

HMNC

Validation of any prognostic test requires strict adherence to study protocol

SOURCES OF MIXED RESULTS FOR ABCB1-TESTING

1. Outpatient vs. Inpatient
2. Multicenter trials
3. Comorbidity
4. Polypharmacy
5. Too high or too low plasma drug levels
6. Weak substrate (e.g. duloxetine)
7. Ethnic background associated with DNA variations

ABCB1-Test
Key facts in a nutshell

- Scientists at the Max-Planck Institute of Psychiatry analysed 95 SNPs within the ABCB1-gene and identified 2 SNPs of particular relevance (rs2032583; rs2235015). Patients carrying the C-allele of SNP2032583 were more likely to remit than in case of the T-genotype.
- A meta-analysis, comprising 16 studies with 2695 patients confirmed a high significance level (1.5×10^{-4}) that rs2932583 in the presence of the C-genotype predicts beneficial response.
- If an antidepressant drug does not act on the disease causing mechanism, it does not work, whatever the ABCB1-test informs. The ABCB1-test closes the gap between plasma drug level and bioavailability in brain tissue.

HMNC

Recommendation for the clinician*

Reasons for poor response to AD	Recommendation
1 Medication is not well resorbed from GI-tract and/or rapidly metabolized	Plasma drug concentration, CYP450 isoenzymes
2 Medication does not sufficiently penetrate into brain tissue	ABCB1-Test
3 The antidepressant mode of action does not target the specific causal mechanism	Switch to an AD with a different mode of action or Combination of different antidepressants, antipsychotics or mood stabilizer

* The Swiss Society of Anxiety and Depression (SGAD) recommends officially in their guuielines to administer the ABCB1-test for optimizing treatment of acute depression, whenever the patient fails to respond within 2-4 weeks.

HMNC

Personalized Medicine: A glimpse to the future

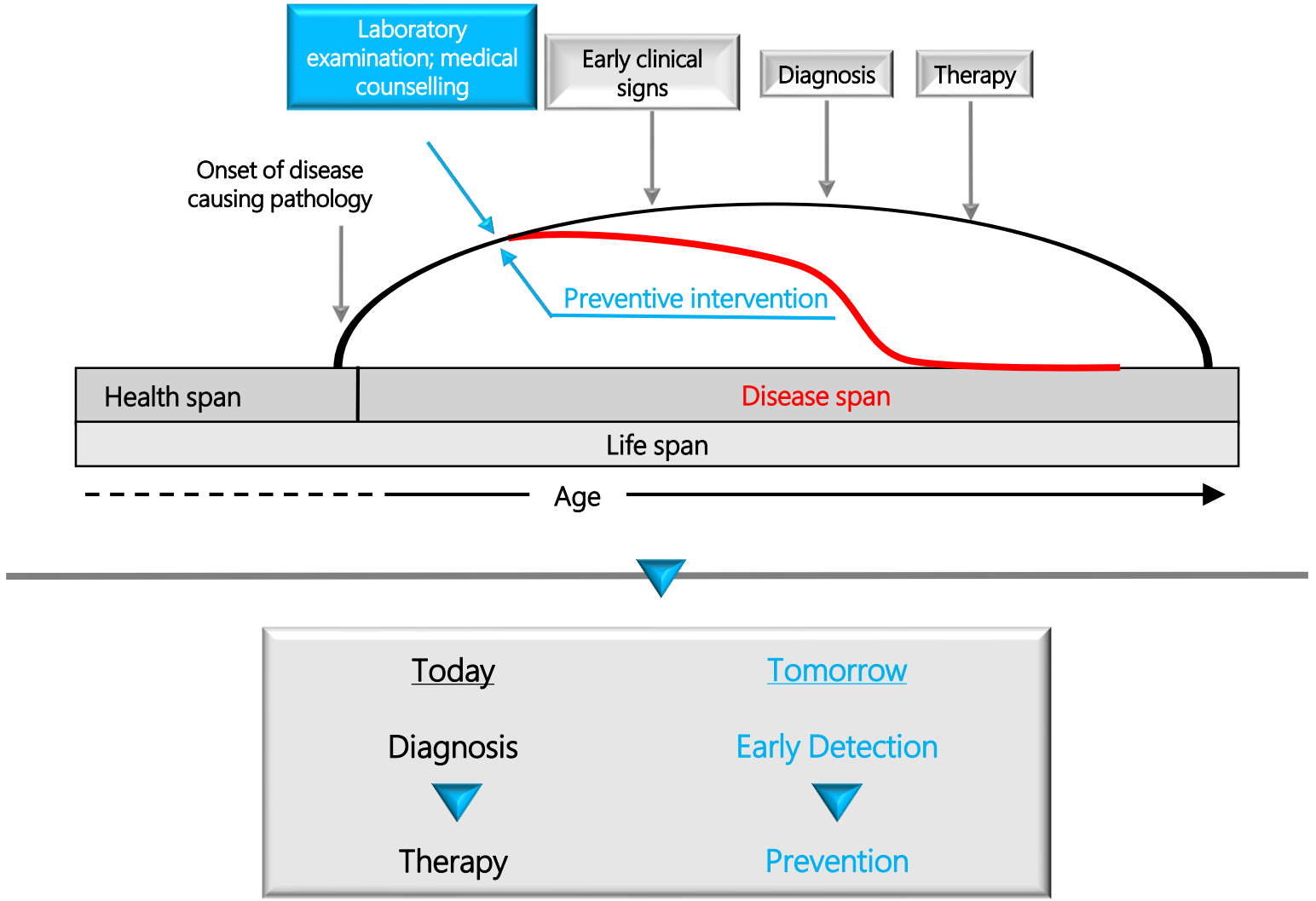
- In the future personalized medicine will enable individual treatments that prevent development of pathology at an early stage before clinical signs occur.

▶ PREVENTIVE MEDICINE replaces REPAIR MEDICINE

Key Players:

- Genetics and genomics (trait)
- Biomarkers (state)
- „Big-data“ – based algorithms

The Future: Paradigm Shift



HMNC Brain Health

We thank you for your interest!

Florian Holsboer

HMNC Holding GmbH · Wilhelm-Wagenfeld-Straße 20 · 80807 München
www.hmnc.de