# Die Evidenz für den **klinischen** Benefit der Pharmakogentik wird immer stärker

| | | |
|---|---|---|
| 2019,<br>Seven of University of Florida Health primary care clinics,<br>375 enrolled patients [1)] | Within the same subgroup of IM/PMs prescribed tramadol or codeine at baseline, CYP2D6-guided group experienced a **30% reduction in composite pain intensity** compared with the usual care group. | PAIN |
| 2019,<br>Meta-analysis of 5 randomized controlled trials (RCT),<br>1737 participants across five RCTs [2)] | Pharmacogenetic-guided therapy **1.71 times more likely** to achieve **symptoms remission** relative to individuals who received usual treatment. | mixed |
| 2016,<br>Netherlands Cancer Inst., Slotervaart Hospital, Canisius Wilhelmina Hospital,<br>2038 patients [3)] | The risk of 5-FU-induced toxicity was significantly reduced **from 73%** in historical controls (n = 48) **to 28% by genotype-guided dosing** (P < .001); drug-induced death was reduced from 10% to 0%. | ONKO |
| 2015,<br>AssureRx Health, Mayo Clinic,<br>258 patients [4)] | Gene-guided treatment raised the odds of **clinical response by 2.3-fold**, the guided group had a **53% greater improvement** in depressive symptoms. | PSYCH |

1. Smith DM, et al., Genet Med. 2019;0(0)., 2. Bousman CA, Arandjelovic K, Mancuso SG, Eyre HA, Dunlop BW., Pharmacogenomics. 2019;20(1):37–47.
3. Deenen MJ, et al., J Clin Oncol. 2016; 34(3):227–34., 4. Altar CA, Carhart J, Allen JD, Hall-Flavin D, Winner J, Dechairo B., Mol Neuropsychiatry. 2015; 1(3):145–55.

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# Der **ökonomischen** Benefit der Pharmakogentik ist ebenfalls belegt

| | | |
|---|---|---|
| 2015,<br>Assurex Health, Mason,<br>Prosp. generated cohort,<br>2168 cases, 10,880 contr. [1)] | Patients receiving **PGx testing saved $1035.60 in total medication** costs over 1 year compared to the usual care cohort (P = 0.007). PGx testing **improved adherence** compared to standard of care. | better adherence |
| 2016,<br>AltheaDx, San Diego [2)] | Applying PGx guided recommendations across the patient population resulted in the **elimination and/or replacement of one to three drugs** and an estimated annual **saving of US$621 per patient**. | less drugs |
| 2015,<br>College of Pharmacy,<br>University of Utah,<br>1025 patients [3)] | Pre-emptive screening via panel-based approach resulted in a signif. **reduction in hospitalizations** (9.8% vs 16.1%, P = 0.027) and patient **visits to the emergency** department (4.4% vs 15.4%, P = 0.0002). | less hospital |
| 2010,<br>Medco Health Solutions,<br>Mayo Clinic,<br>3584 patients [4)] | CYP2C9 and VKORC1 genotyping of warfarin recipients resulted in **31% fewer hospitalizations** overall and a **43% lower risk** of hospitalization for bleeding or thromboembolism. | less hospital |

1. Winner JG, et al. Curr Med Res Opin. 2015;31(9):1633–43. , 2. Saldivar JS, et al. Pharmgenomics Pers Med. 2016;9:1–6.,
3. Brixner D, et al., J Med Econ. 2016;19(3):213–28., 4. Epstein RS, et al., J Am Coll Cardiol. 2010;55(25):2804–12.

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# Bsp: **Clopidogrel**:
# Weniger als die Hälfte der Europ. Bevölkerung ist normaler Metabolisierer für CYP2C19, welches das Pro-Drug Clopidogrel aktiviert

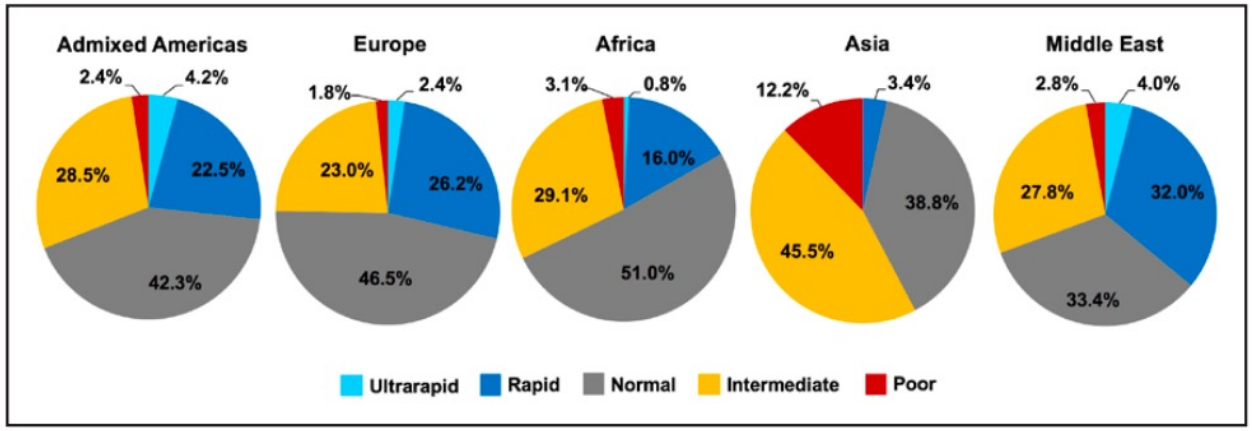


**Figure.** Population frequency estimates of CYP2C19 metabolizer phenotypes by geographic region. Estimates derived from a meta-analysis of 52 181 healthy volunteers from 138 original research articles.[18] Admixed Americas include data from studies conducted in North, Central, and South America.

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# NEJM: Studie mit 2485 Patienten mit perkutaner Koronarintervention

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## A Genotype-Guided Strategy for Oral $P2Y_{12}$ Inhibitors in Primary PCI

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ABSTRACT

**BACKGROUND**

It is unknown whether patients undergoing primary percutaneous coronary intervention (PCI) benefit from genotype-guided selection of oral $P2Y_{12}$ inhibitors.

**METHODS**

We conducted a randomized, open-label, assessor-blinded trial in which patients undergoing primary PCI with stent implantation were assigned in a 1:1 ratio to receive either a $P2Y_{12}$ inhibitor on the basis of early *CYP2C19* genetic testing (genotype-guided group) or standard treatment with either ticagrelor or prasugrel (standard-treatment group) for 12 months. In the genotype-guided group, carriers of *CYP2C19**2 or *CYP2C19**3 loss-of-function alleles received ticagrelor or prasugrel, and noncarriers received clopidogrel. The two primary outcomes were net adverse clinical events — defined as death from any cause, myocardial infarction, definite stent thrombosis, stroke, or major bleeding defined according to Platelet Inhibition and Patient Outcomes (PLATO) criteria — at 12 months (primary combined outcome; tested for noninferiority, with a noninferiority margin of 2 percentage points for the absolute difference) and PLATO major or minor bleeding at 12 months (primary bleeding outcome).

**RESULTS**

For the primary analysis, 2488 patients were included: 1242 in the genotype-guided group and 1246 in the standard-treatment group. The primary combined outcome occurred in 63 patients (5.1%) in the genotype-guided group and in 73 patients (5.9%) in the standard-treatment group (absolute difference, −0.7 percentage points; 95% confidence interval [CI], −2.0 to 0.7; P<0.001 for noninferiority). The primary bleeding outcome occurred in 122 patients (9.8%) in the genotype-guided group and in 156 patients (12.5%) in the standard-treatment group (hazard ratio, 0.78; 95% CI, 0.61 to 0.98; P=0.04).

**CONCLUSIONS**

In patients undergoing primary PCI, a *CYP2C19* genotype–guided strategy for selection of oral $P2Y_{12}$ inhibitor therapy was noninferior to standard treatment with ticagrelor or prasugrel at 12 months with respect to thrombotic events and resulted in a lower incidence of bleeding. (Funded by the Netherlands Organization for Health Research and Development; POPular Genetics ClinicalTrials.gov number, NCT01761786; Netherlands Trial Register number, NL2872.)

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1245 PCI Pat

Standard:

Ticagrelor or Prasugrel

1240 PCI Pat

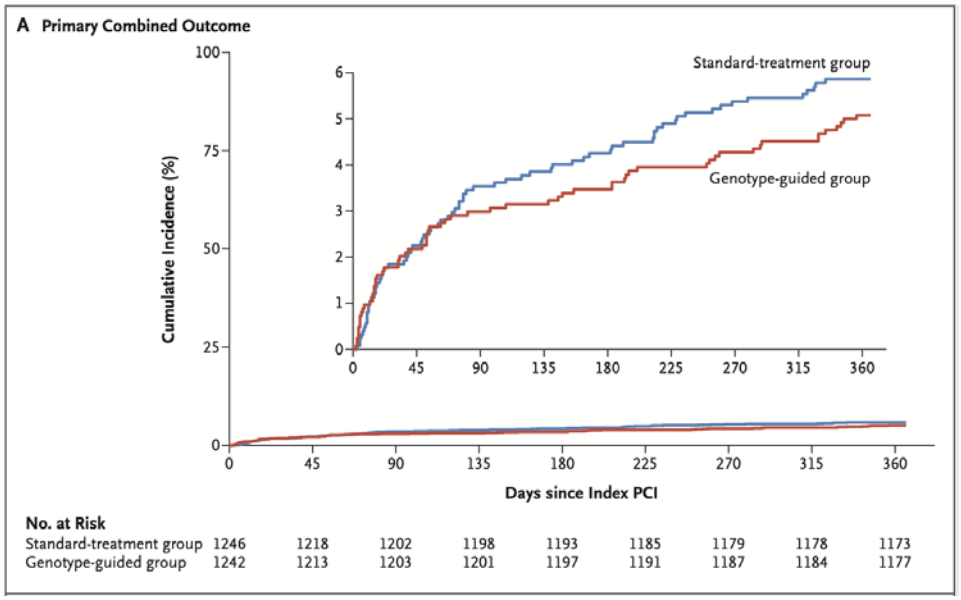
Genotype-guided:

Clopidogrel

Cyp2C19 loss of function

Ticagrelor or Prasugrel

# Primary Combined Outcome (thrombotic & bleeding): non-inferior
# Primary Bleeding Outcome: Vorteil für Genotyp-guided group (p= 0,04)



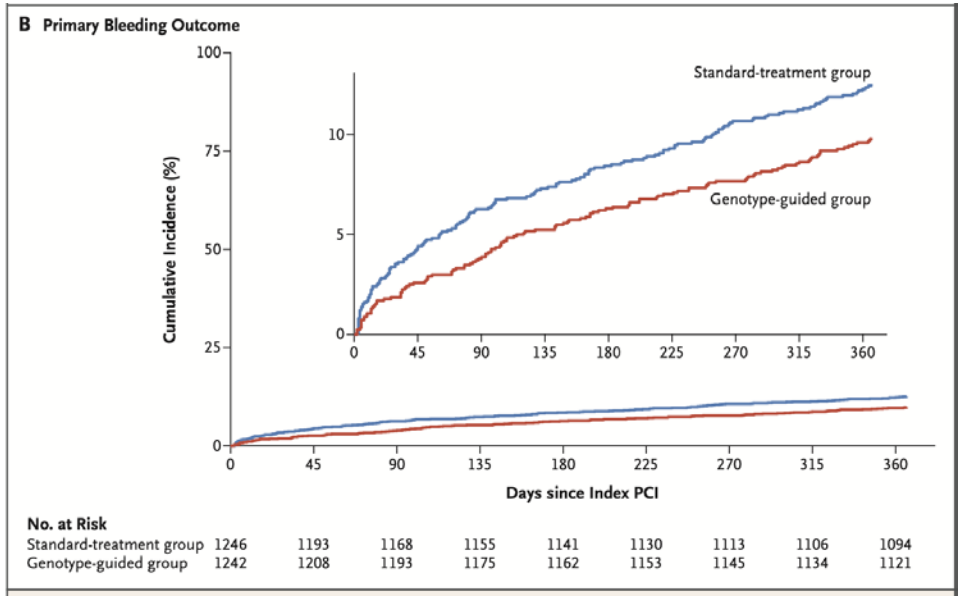




**Figure 2. Incidence Curves for the Primary Outcomes.**

Panel A shows the cumulative incidence of the primary combined thrombotic and bleeding outcome, consisting of death from any cause, myocardial infarction, definite stent thrombosis, stroke, or major bleeding defined according to Platelet Inhibition and Patient Outcomes (PLATO) criteria. Panel B shows the primary bleeding outcome of PLATO major or minor bleeding. The inset in each panel shows the same data on an enlarged y axis. PCI denotes percutaneous coronary intervention.

**Table 3. Primary and Secondary Bleeding Outcomes.***

| Outcome | Genotype-Guided Group (N=1242) | Standard-Treatment Group (N=1246) | Hazard Ratio (95% CI) | P Value |
|---|---|---|---|---|
| | *no. of patients (%)* | | | |
| Primary bleeding outcome: PLATO major or minor bleeding | 122 (9.8) | 156 (12.5) | 0.78 (0.61–0.98) | 0.04† |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# Bsp: **5-Fluorouracil (5-FU),** Capecitabin und Tegafur
# Seit Apr. 2020 verpflichtende PGx-Testung!


DPD Testung
25. Mai 2020

DGHO

in Kooperation mit

BNHO

Deutsche Gesellschaft für Senologie

DGVS
Deutsche Gesellschaft für Gastroenterologie, Verdauungs- und Stoffwechselkrankheiten

DKG KREBSGESELLSCHAFT

gfh
Deutsche Gesellschaft für Humangenetik

OeGHO

SSMO SSOM SGMO

**Positionspapier**

Dihydropyrimidin-Dehydrogenase (DPD) -Testung vor Einsatz von 5-Fluorouracil, Capecitabin und Tegafur

Mai 2020

- Prävalenz der relevanten DPD-Genvarianten:
  - ca. 9% verminderte DPD Aktivität
  - ca. 0,5% vollständiger DPD Mangel

  } Risiko für schwere Nebenwirkungen
- **EMA** empfiehlt bei jedem Patienten vor Therapie die Genvarianten zu prüfen
- Ist bereits in der **Fachinformation** enthalten
- **Positionspapier** der Onkologischen Gesellschaften (Mai 2020)

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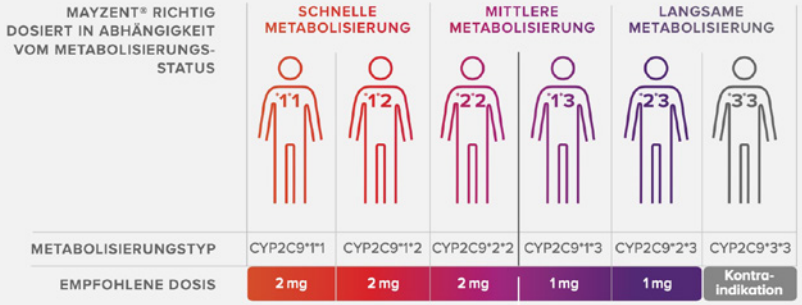
# Bsp: **Siponimod** (Mayzent) bei Multipler Sklerose: Verpflichtender PGx-Test vor Therapie-Start

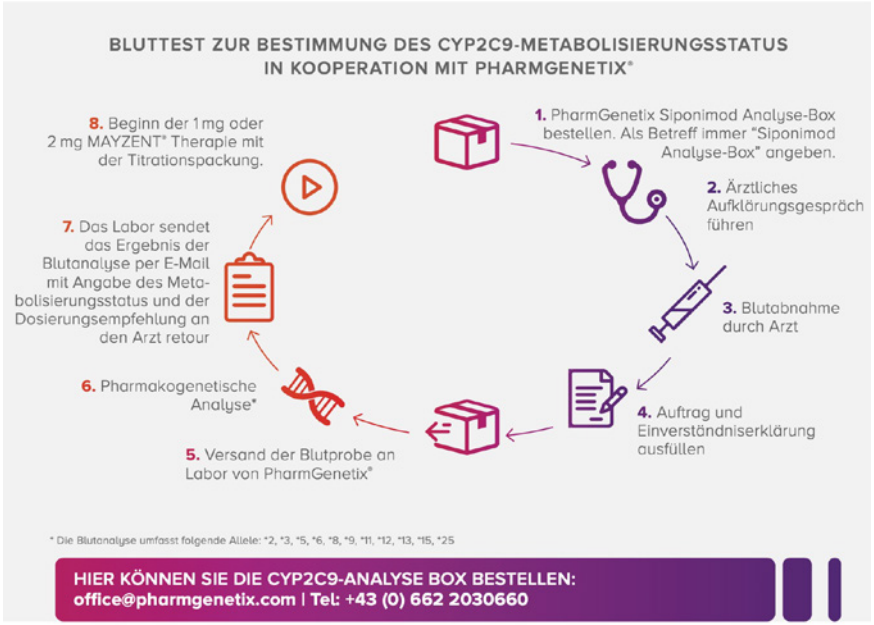
## DER METABOLISIERUNGSSTATUS BESTIMMT DIE MAYZENT®-DOSIS

MAYZENT® (Siponimod) wird täglich in Form von Filmtabletten vom Patienten eingenommen. Die Metabolisierung von MAYZENT® (Siponimod) erfolgt über CYP2C9. Vor Beginn einer Behandlung mit MAYZENT® (Siponimod) muss daher bei den Patienten der CYP2C9-Metabolisierungsstatus bestimmt werden.




MAYZENT siponimod

## METABOLISIERUNGSSTATUS ZUR BESTIMMUNG DER PASSENDEN THERAPIE



# Bsp: **Psychopharmaka**: Die Genetik des S(S/N)RI Abbaus ist sehr variantenreich

| WIRKSTOFF | MEDIKAMENT | ABBAU I - primär I - sekundär I - beteiligt |
|---|---|---|
| Citalopram #+§ ! | Pram, Seropram, Citalostad, Celexa, Ran-Citalo | **CYP2C19**<br>CYP3A4 |
| Duloxetin ! | Dulasolan, Yentreve, Cymbalta | **CYP2D6**<br>**CYP1A2** |
| Escitalopram +§ | Cipralex, Lexapro, Pramulex | **CYP2C19, CYP2D6**<br>CYP3A4 |
| Fluoxetin ! | Felicium, Mutan, Prozac, Sarafem, FXT, Fluoxibene | **CYP2D6**<br>**CYP2C9** |
| Fluvoxamin + | Luvox, Riva-Fluvox, Floxyfral | **CYP2D6**<br>CYP1A2 |
| Mirtazapin | Mirtabene, Mirtel, Mirtaron | **CYP2D6**<br>**CYP3A4,** CYP1A2 |
| Paroxetin #+§ ! | Seroxat, Paxil, Pexeva, Parocetan, Ennos | **CYP2D6,** CYP2C19<br>**CYP3A4,** CYP1A2<br>CYP3A5 |
| Sertralin +§ ! | Gladem, Tresleen, Adjuvin, Zoloft | **CYP2C19**<br>**CYP2B6,** CYP3A4 |
| Venlafaxin § | Efectin, Effexor | **CYP2D6, CYP2C19**<br>**CYP3A4** |


## CYP2D6

- Punktmutationen
- Strukturelle Variationen
  - Gen Duplikationen
  - Gen Vervielfachung
  - Gen Deletionen
  - 2D6/2D7 Hybride