genomDE-Symposium

Perspektiven der Genommedizin jenseits von seltenen Erkrankungen und Krebs

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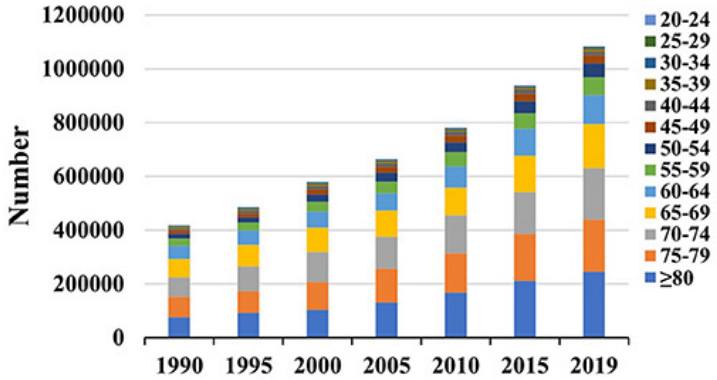
Institut für Neurogenetik, Universität zu Lübeck und Universitätsklinikum Schleswig-Holstein

7. Juli 2022

M. Parkinson ist häufig und ansteigend



- Ca. 10 Mio. Erkrankte weltweit
- Inzidenz ca. 1 Mio./Jahr
- Am schnellsten wachsende neurologische Erkrankung weltweit

M. Parkinson – eine genetische Erkrankung?

SNCA

Parkin

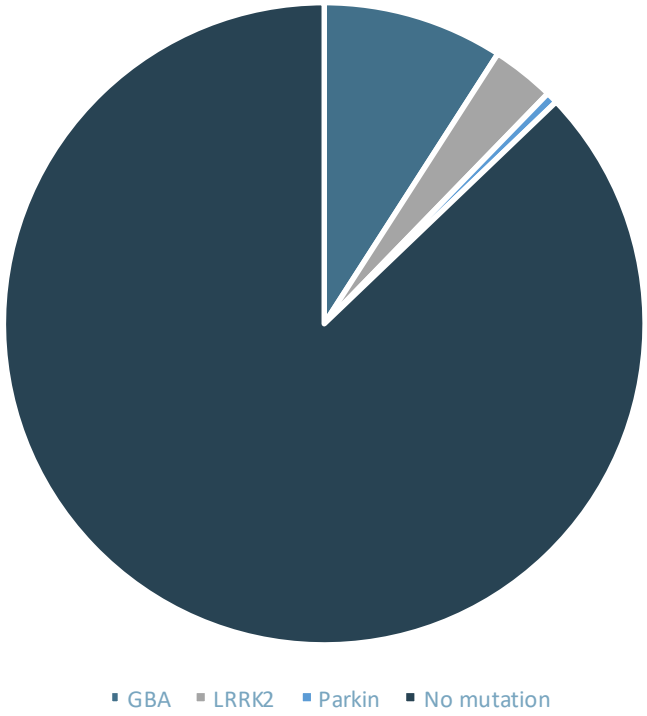
LRRK2

PINK1

VPS35

GBA

M. Parkinson: ca. 10 % genetisch



>13,000 Patienten

Einschluss in klinische Studien:

- **Parkinson-Studie: 1 Pat. alle 4 Tage**
- **Huntington-Studie: 4 Pat. pro Tag**

Skrahina et al. Mov Disord 2020

Ein Phänotyp – viele Gene

SNCA

Parkin

LRRK2

PINK1

VPS35

GBA

Ein Gen – viele Phänotypen

PINK1

Video courtesy of
A. Al-Rumayyan and
M. Alfadhel

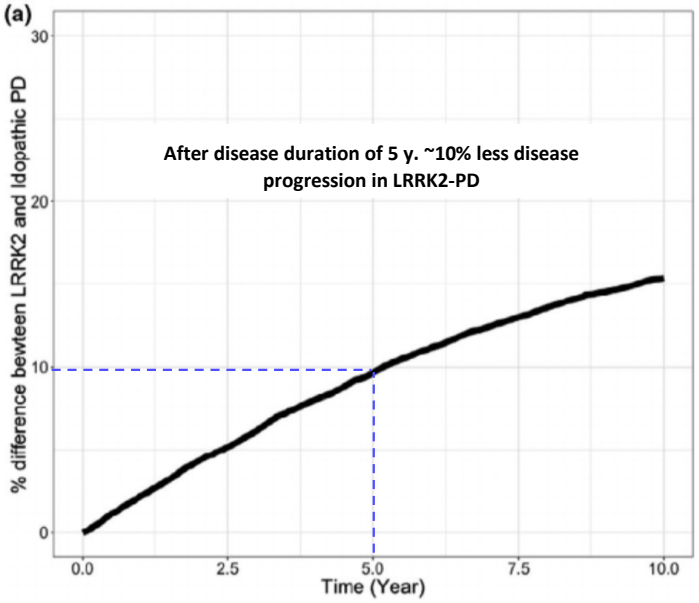
M. Parkinson: Aktuelle klinische Studien

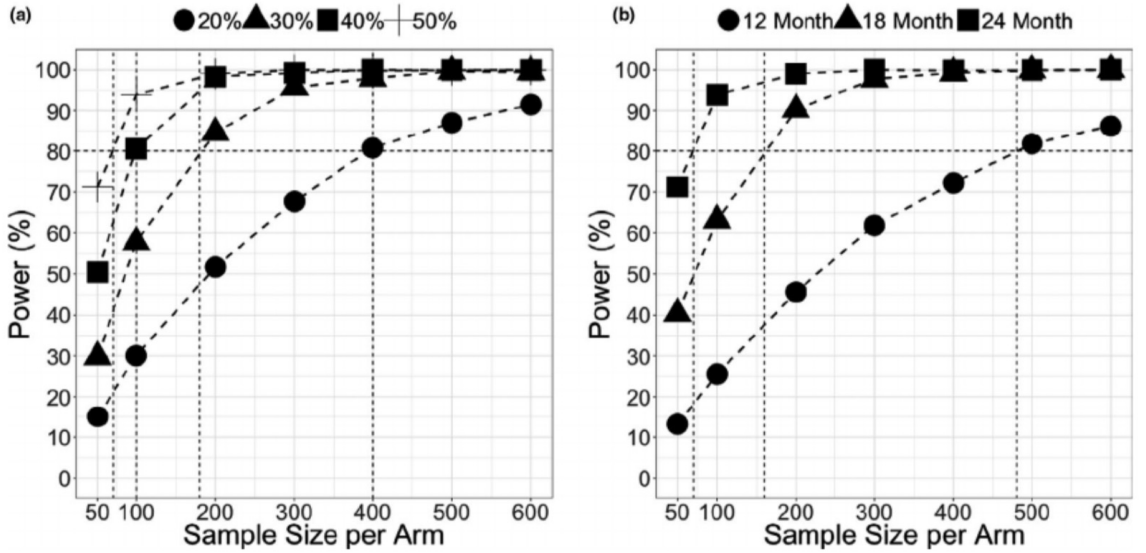
Table 2 Active clinical trials targeting distinct pathways in Parkinson's disease patients

Trial name	Registration number	Study design	Outcomes	Study participants
α-Synuclein aggregation				
Impact of Bosutinib on safety, tolerability, biomarkers and clinical outcomes in dementia with lewy bodies	NCT03888222	MonoC, DB, R, PC	1st: Safety and tolerability	DLB patients
Single ascending dose study of MEDI1341 in healthy volunteers	NCT03272165	MultiC, DB, R, PC	1st: Safety and tolerability	HVs
Endosomal/lysosomal dysfunction				
A study to evaluate the safety, tolerability, and pharmacokinetics of BIIB094 in adults with Parkinson's disease (REASON)	NCT03976349	MultiC, DB, R, PC	1st: Safety and tolerability	mPD (*LRRK2*), IPD patients
A study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of DNL151 in healthy volunteers	NCT04557800	MultiC, DB, R, PC	1st: Safety and tolerability	HVs
Study to evaluate DNL151 in subjects with Parkinson's disease	NCT04056689	MultiC, DB, R, PC	1st: Safety and tolerability	PD patients
Study to evaluate DNL201 in subjects with Parkinson's disease	NCT03710707	MultiC, DB, R, PC	1st: Safety and tolerability	mPD (*LRRK2*), IPD patients
Phase 1/2a clinical trial of PR001A in patients with Parkinson's disease with at least one GBA1 mutation (PROPEL)	NCT04127578	MultiC, DB, R, PC	1st: Safety and tolerability	mPD (*GBA*), IPD patients

Brueggemann and Prasuhn. Mol Med 2021

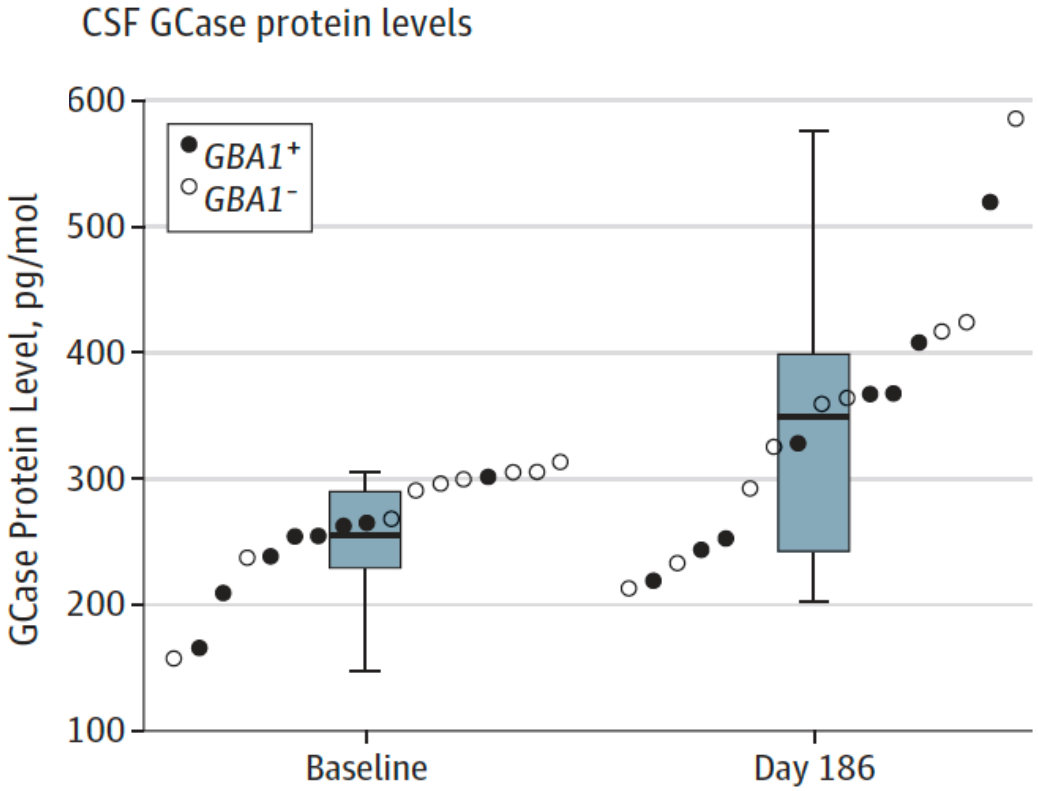
LRRK2: Spezifische Studienplanung





Ahamadi et al. Clin Pharmacol Ther 2020

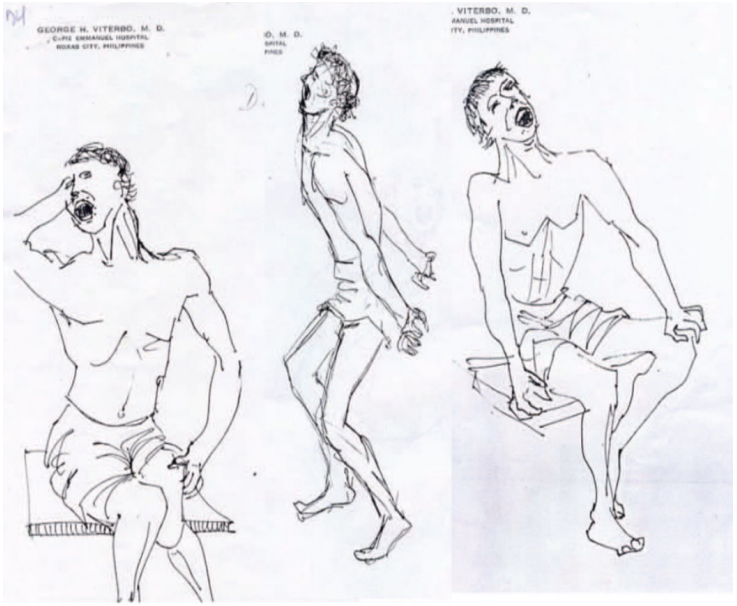
Wirkung bei idiopathischem M. Parkinson?



Ambroxol-Studie

Mullin et al. JAMA Neurol 2020

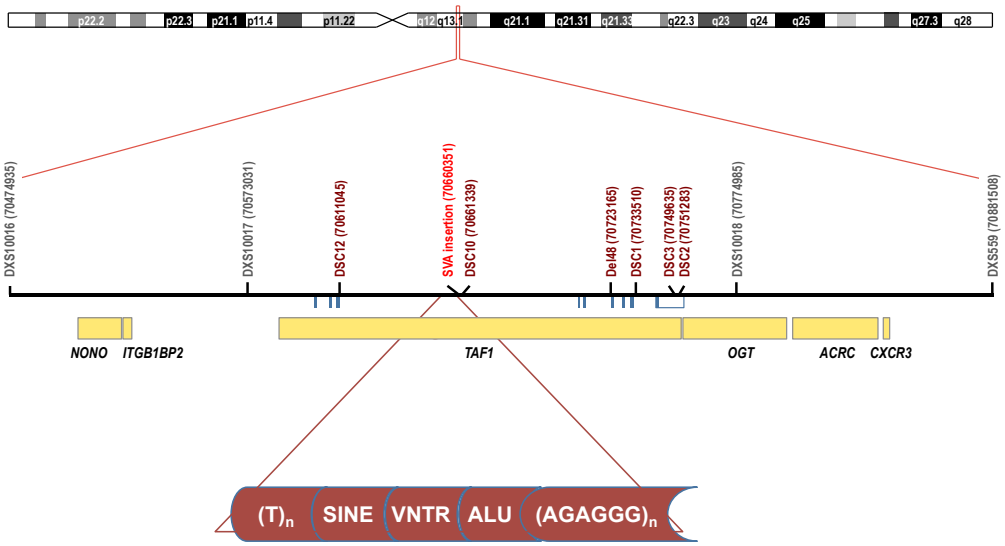
X-chr. Dystonie-Parkinson-Syndrom

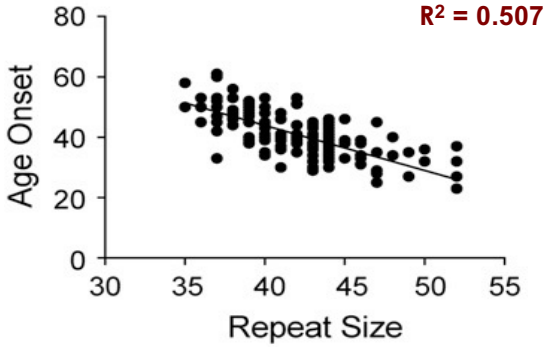


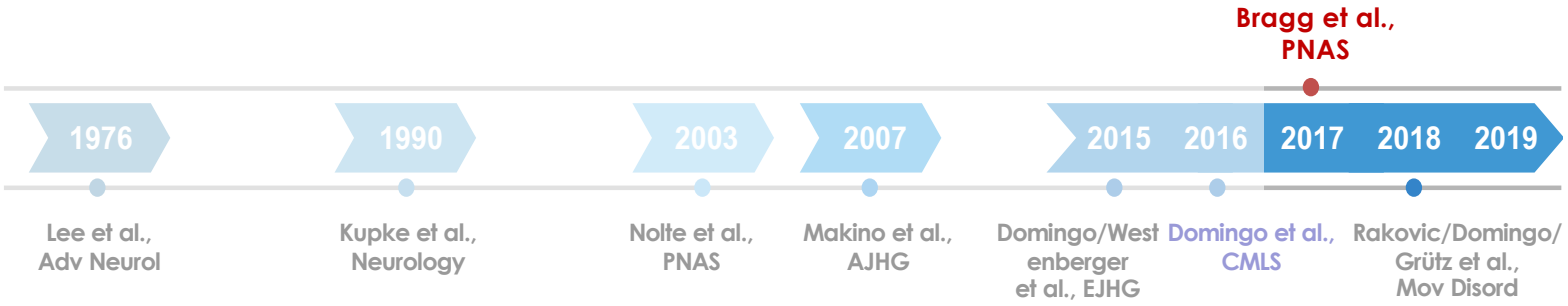
Lee *et al.* 2011. *International Journal of Neuroscience* 121(5): 3-11.

Erkrankungsalter: 12-64 Jahre
(Modifizierende Faktoren, Gentherapie?

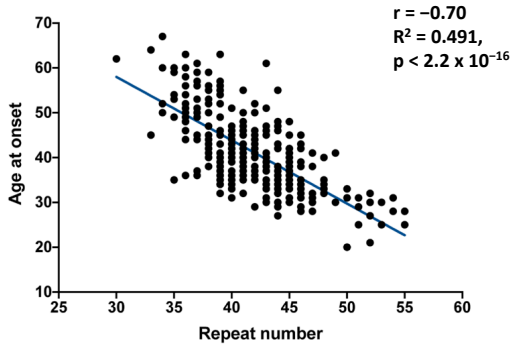
Genetische Einflussfaktoren

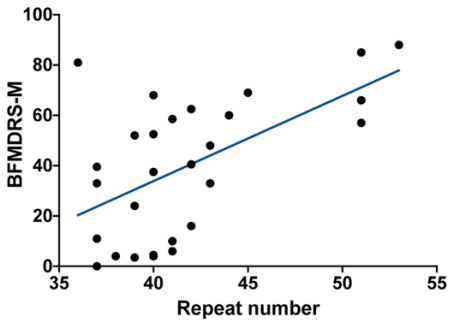


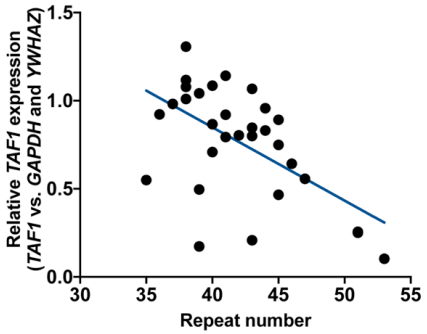


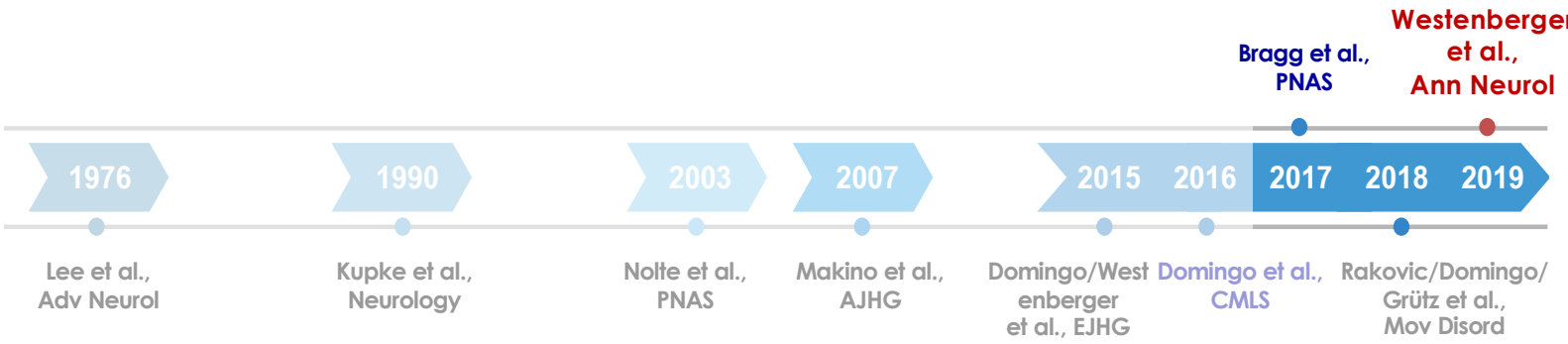


Genetische Einflussfaktoren

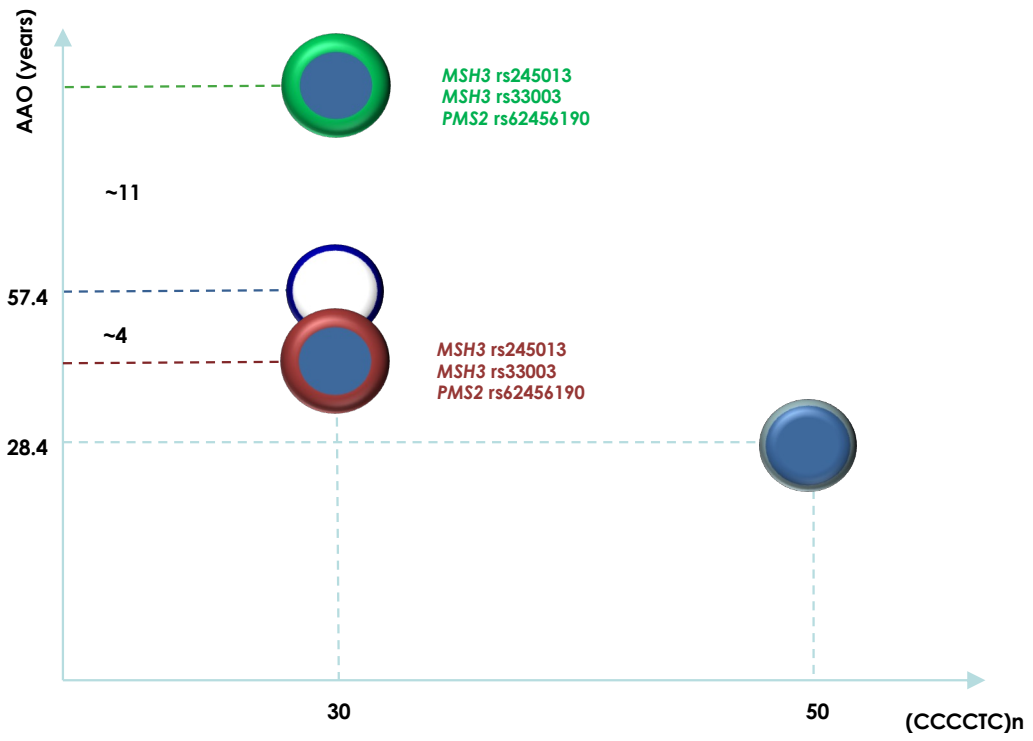








Genomweite Analysen: Persönliche Prognose



Animation von PD Dr. A. Rakovic

Neurodegeneration: Frühe Phasen

Tiefe Hirnstimulation

Beispiel Diabetes

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

An Anti-CD3 Antibody, Teplizumab, in Relatives at Risk for Type 1 Diabetes

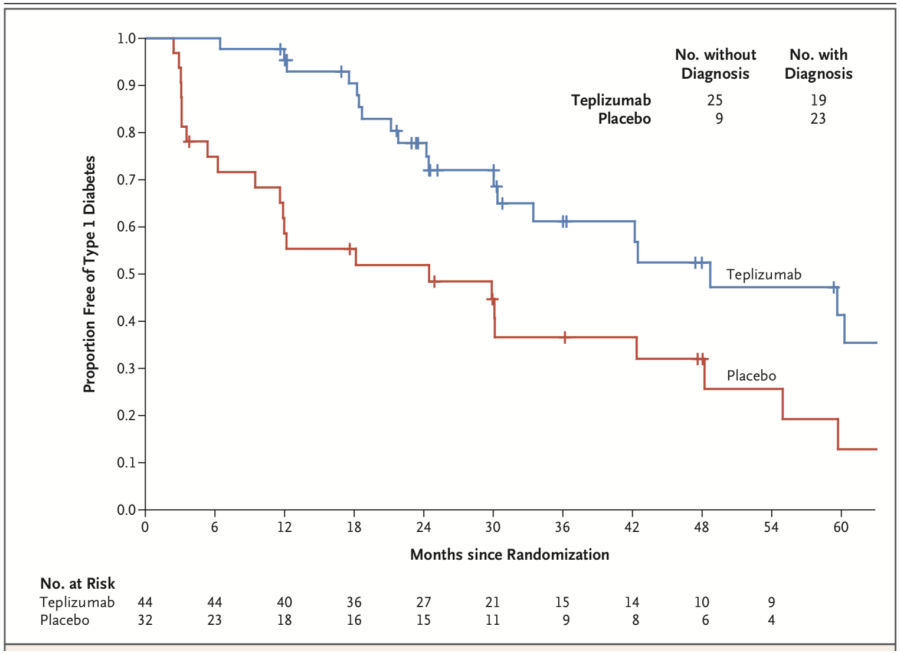
Kevan C. Herold, M.D., Brian N. Bundy, Ph.D., S. Alice Long, Ph.D., Jeffrey A. Bluestone, Ph.D., Linda A. DiMeglio, M.D., Matthew J. Dufort, Ph.D., Stephen E. Gitelman, M.D., Peter A. Gottlieb, M.D., Jeffrey P. Krischer, Ph.D., Peter S. Linsley, Ph.D., Jennifer B. Marks, M.D., Wayne Moore, M.D., Ph.D., Antoinette Moran, M.D., Henry Rodriguez, M.D., William E. Russell, M.D., Desmond Schatz, M.D., Jay S. Skyler, M.D., Eva Tsalikian, M.D., Diane K. Wherrett, M.D., Anette-Gabriele Ziegler, M.D., and Carla J. Greenbaum, M.D., for the Type 1 Diabetes TrialNet Study Group*

Herold et al. NEJM, June 2019; Abbasi JAMA 2021

Behandlung in der prämanifesten Phase

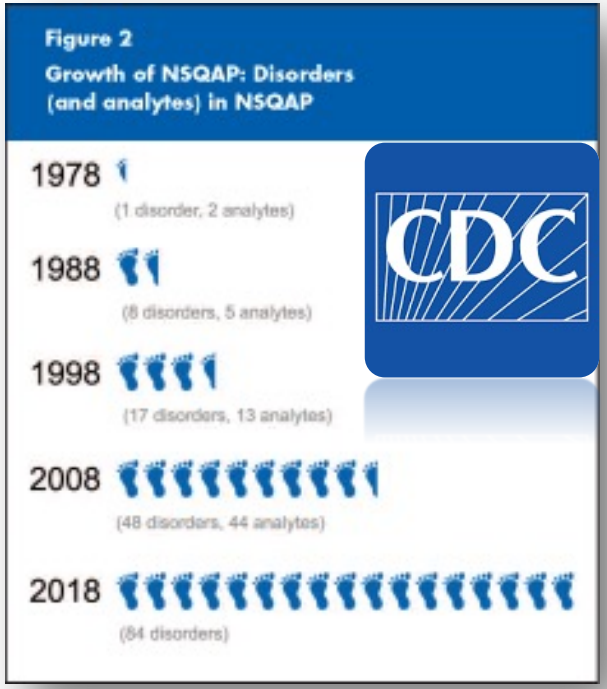
Table 1. Baseline Characteristics of the Participants.*

Characteristic	Teplizumab (N=44)	Placebo (N=32)
Age — yr		
Median (IQR)	14 (12–22)	13 (11–16)
Range	8.5–49.5	8.6–45.0
Age <18 yr — no. (%)	29 (66)	26 (81)
Male sex — %	57	53
Relationship to person with type 1 diabetes — no. (%)		
Sibling†	28 (64)	16 (50)
Offspring	6 (14)	6 (19)
Parent	6 (14)	3 (9)
Sibling and another first-degree relative	2 (5)	3 (9)
Second-degree relative	2 (5)	3 (9)
Third-degree relative or further removed	0	1 (3)
Autoantibodies — no. of participants positive (%)‡		
Anti-GAD65, harmonized	40 (91)	28 (88)
Micro insulin	20 (45)	11 (34)
Anti–IA-2, harmonized	27 (61)	24 (75)
ICA	29 (66)	28 (88)
Anti-ZnT8	32 (73)	24 (75)
Median glycated hemoglobin level (IQR) — %	5.2 (4.9–5.4)	5.3 (5.1–5.4)



Median time to diagnosis:
48.4 months (Teplizumab)
24.4 months (placebo)

Erfolgreiche Idee eines breiten Screenings



Zusammenfassung und Perspektiven

- Wichtige Rolle von Genomsequenzierung auch bei häufigen Erkrankungen
- Gleichzeitige Identifzierung kausaler und modifizierender Faktoren
- Verbesserung der individuellen Prognose (personalisierte Medizin)
- Stratifizierung für klinische Studien und Therapieoptionen
- Langfristig kostengünstigste Alternative
- Kontinuierlicher Wissensgewinn von translationaler Bedeutung
- Erweiterung der Aus- und Fortbildung

Die Zukunft der Neurologen…

Google search (image): Neurologist

Vielen Dank!

www.neurogenetics-luebeck.de