



Rett Familientreffen, 25. Juni 2022, Hipping

Was gibt es Neues - gibt es was Neues?

AO UNIV.- PROF. DR. MICHAEL FREILINGER



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COVID

rettsym
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ome.org

ABOUT RETT SYNDROME FOR FAMILIES GET INVOLVED ASCEND NATIONAL SUMMIT RE
ABOUT US

DATE: Best practices according to our

SHARE OUR SITE ON      SPRACHE AUS

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J22 Rett
Summit

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Syndrome

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Rett
Meeting

COVID UPDATE: Best practices according to medical expert

December 10, 2021
Categories: Blog, Homepage, News

As the COVID pandemic continues with surges and new variants, we have asked IRSF Medical, Tim Benke, Rett Clinic Medical Director at Children's Hospital Colorado, to provide information COVID-19 to keep our families and community healthy and safe at this time.

Vaccinations:

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Fragebogen Studie "Altern mit Rett Syndrome"

Projektplan

„Älter werden mit Rett Syndrom“

Eine Fragebogenstudie

Analyse der österreichischen Rett-Patientinnen und Vergleich mit der niederländischen Rett-Kohorte

Klara Marschütz

01442114

Universitätsklinik für Kinder- und Jugendheilkunde der
Medizinischen Universität Wien
Ao. Univ.-Prof. Dr. Michael Freilinger

► Danke

 MEDIZINISCHE
UNIVERSITÄT WIEN

Diplomarbeit

„Älter werden mit Rett Syndrom“

Fragebogenstudie zur Erhebung der Lebenssituation
von Patientinnen mit Rett Syndrom in Österreich

zur Erlangung des akademischen Grades

Doktorin der gesamten Heilkunde

(Dr. med. univ.)

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Clarke and Abdala Sheikh *Orphanet Journal of Rare Diseases* (2018) 13:44
<https://doi.org/10.1186/s13023-018-0786-6>

Orphanet Journal of
Rare Diseases

POSITION STATEMENT

Open Access

A perspective on “cure” for Rett syndrome



Angus John Clarke^{1,3*} and Ana Paula Abdala Sheikh²

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When Will We Have a Cure?

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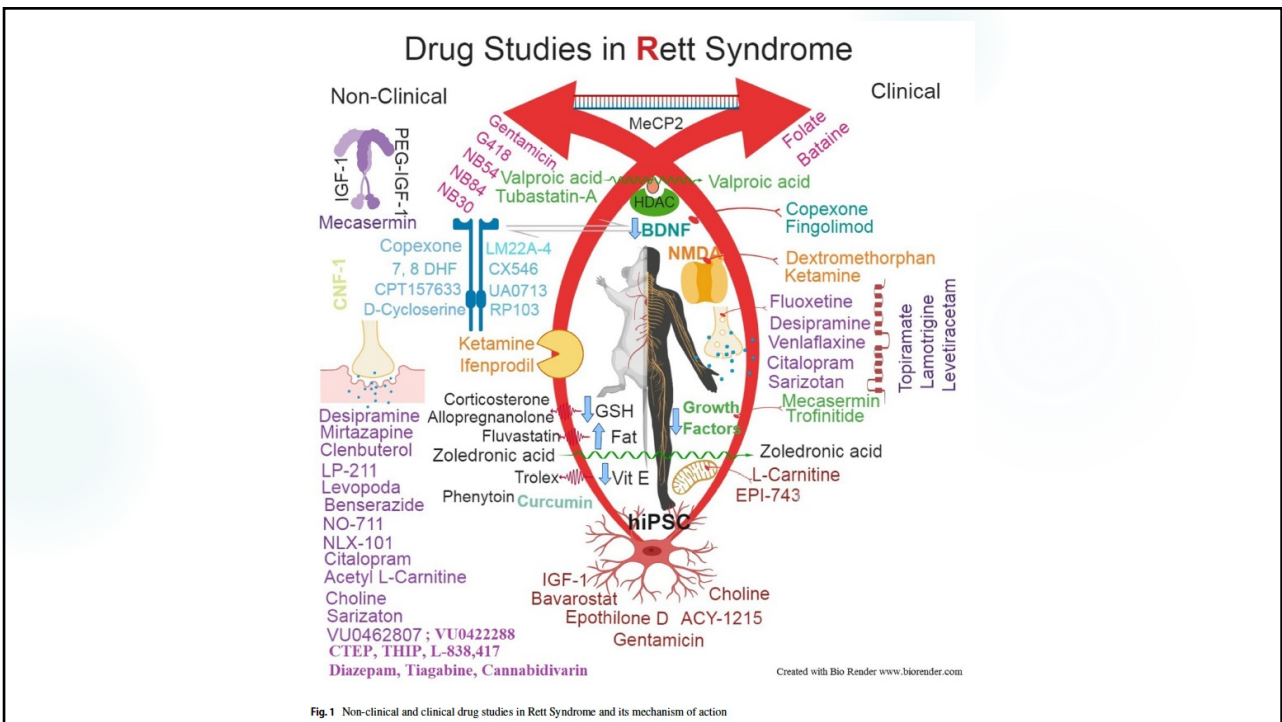


Fig. 1 Non-clinical and clinical drug studies in Rett Syndrome and its mechanism of action

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	Preclinical outcomes	Clinical outcomes
BDNF augmenters		
Fingolimod	Increases BDNF concentration, locomotor activity, and striatal size in a mouse model of Rett syndrome ⁴⁸	Trial completed, no results published yet (0-25 mg vs 0.5 mg; primary outcome measure, BDNF concentrations in the blood and cerebrospinal fluid before and during treatment measured for 12 months, n=6; NCT02061137)
IGF-1 augmenters		
Clenbuterol (β2-adrenergic agonist)	Increases endogenous IGF-1, extends survival in mice with Rett syndrome ⁴⁹	No trial yet
Mecasermin (human recombinant IGF-1)	Improves breathing abnormalities, reduces anxiety in mice with Rett syndrome ⁵⁰	Safe in girls, might ameliorate breathing abnormalities (12 girls with MECP2 mutations, nine with Rett syndrome; NCT01252317) ⁵¹ might have no clinical effect (crossover trial, n=30; NCT01777542) ⁵²
Trofinetide (terminal tripeptide of IGF-1)	Trofinetide improves locomotor function, breathing, heart rate, and lifespan of Mecp2 null mice ⁵³	Safe in girls, some efficacy shown in early small studies (n=56, randomly assigned in dose-escalation trial) ⁵⁴ ; ongoing efficacy (NCT04181723) and safety tolerability (NCT04279314) studies
GABAergic modulators		
Picrotoxin (GABA _A antagonist)	Improves motor coordination and episodic memory in mouse model of MECP2 duplication syndrome ⁵⁵	No trial yet
Glutamatergic modulators		
Ketamine (NMDA receptor antagonist)	Improves cortical function and extends life span of mice with Rett syndrome ⁵⁶	Clinical trial ongoing (estimated enrolment 48 participants; NCT03633058)
Dextromethorphan (NMDA receptor antagonist)	No animal studies	Dose-dependent improvement in seizures, receptive language, and behavioural hyperactivity (n=35, open-label trial, no placebo group; NCT00553557) ⁵⁷
α-1 agonist		
Anavex 2-73 (blarcamesine)	Female heterozygous Rett syndrome mice have improved motor coordination, balance, acoustic and visual responses, and respiration ⁵⁸	Multiple clinical studies ongoing (NCT04304482; NCT03941444; NCT03758924)
Aminergic agents		
Levodopa dopa-decarboxylase (dopaminergic)	Improves mobility and breathing in Rett syndrome mouse model ⁵⁹	No trial yet
Sarizotan (serotonin 1A receptor agonist/D, partial agonist)	Corrects irregular breathing and apnoea in mouse model of Rett syndrome ⁶⁰	Sarizotan (estimated enrolment 129 participants, 2-10 mg per day vs placebo; completed, results awaited; NCT02790034)
Metabolic interventions		
Triheptanoin	Improves motor function, longevity and biochemical markers in a mouse model of Rett syndrome ⁶¹	Clinical trial ongoing (estimated enrolment 12 participants, single group; NCT02696044)
Vatiquinone	Improves mitochondrial function	Phase 2 study completed, no published results (24 enrolled participants, 600/743 15 mg/kg per day vs placebo; NCT01822249)
Neuronal stimulation		
Deep brain stimulation (fornical)	Improves spatial learning and memory in mice with Rett syndrome ⁶²	No trial yet
Genetic manipulation		
Gene replacement (in Rett syndrome)	Reverses molecular and behavioural deficits of Rett syndrome ⁶³	No trial yet
Antisense oligonucleotides to suppress Mecp2 levels (in MECP2 duplication syndrome)	Reverses molecular and behavioral deficits of MECP2 duplication syndrome ⁶⁴	Clinical readiness trials ongoing
CRISPR-Cas9 genetic engineering (in Rett syndrome)	Repair of mutation in human pluripotent stem cells ⁶⁵	No trial yet

Table 3: Therapeutic interventions that seek to address underlying defects in Rett syndrome and MECP2 duplication syndrome

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Experimentelle Therapien

AMO-04

AMO-04 is an antidepressant being repurposed to potentially treat Rett syndrome. The active compound in AMO-04, is tianeptine, an antidepressive agent. It is a molecule that modulates the action of the neurotransmitter glutamate, vital to brain development and neuronal function. The potential therapy showed promise in animal models of Rett syndrome, but it has not yet been tested in patients with the disease.

[LEARN MORE](#)

- ▶ Tianeptin
- ▶ Antidepressivum
- ▶ Glutamat Rezeptor
- ▶ BDNF
- ▶ Mausstudien

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Experimentelle Therapien

Anavex 2-73

Anavex 2-73 is an investigational small molecule that targets a protein receptor called the sigma-1 receptor. This is a so-called chaperone, in that it guides newly synthesized proteins through a compartment in the cell called the endoplasmic reticulum, ensuring they fold correctly. By binding and activating this receptor, Anavex 2-73 may be able to reduce protein misfolding, potentially easing Rett symptoms. It is currently being tested in a Phase 2/3 trial.

[LEARN MORE](#)

- ▶ Anavex
- ▶ Blarcamesine
- ▶ Anavex 2-73 is a small molecule that targets a protein receptor called the sigma-1 receptor. This is a so-called chaperone, in that it guides newly synthesized proteins through a compartment in the cell called the endoplasmic reticulum, ensuring they fold correctly.
- ▶ Phase II – Studie laufend

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Experimentelle Therapien

AVXS-201

For Rett syndrome, scientists are researching a gene therapy approach, in which the correct versions of the *MECP2* gene can be delivered into the nucleus of cells in the brain. AVXS-201 is an investigational gene therapy that is being developed to deliver a healthy form of the *MECP2* gene via a viral vector in such a way that it can provide MeCP2 protein in sufficient quantities after delivery. It is still in the preclinical stage, with the hope of launching an in-human trial soon.

[LEARN MORE](#)

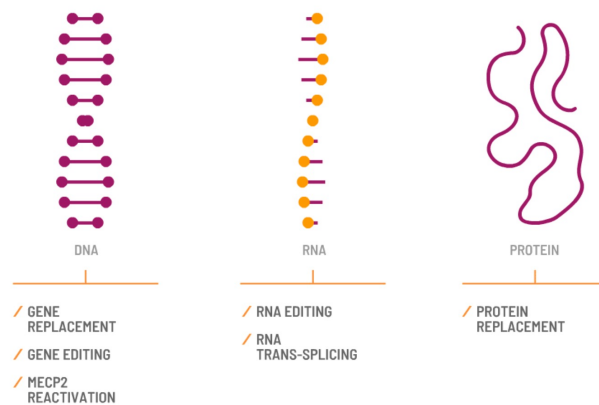
- ▶ OAV201, formerly AVXS-201
- ▶ OAV201 uses a category of viruses called [adeno-associated virus 9 \(AAV9\)](#) as vectors or carriers for the normal human *MECP2* gene
- ▶ Mausmodell

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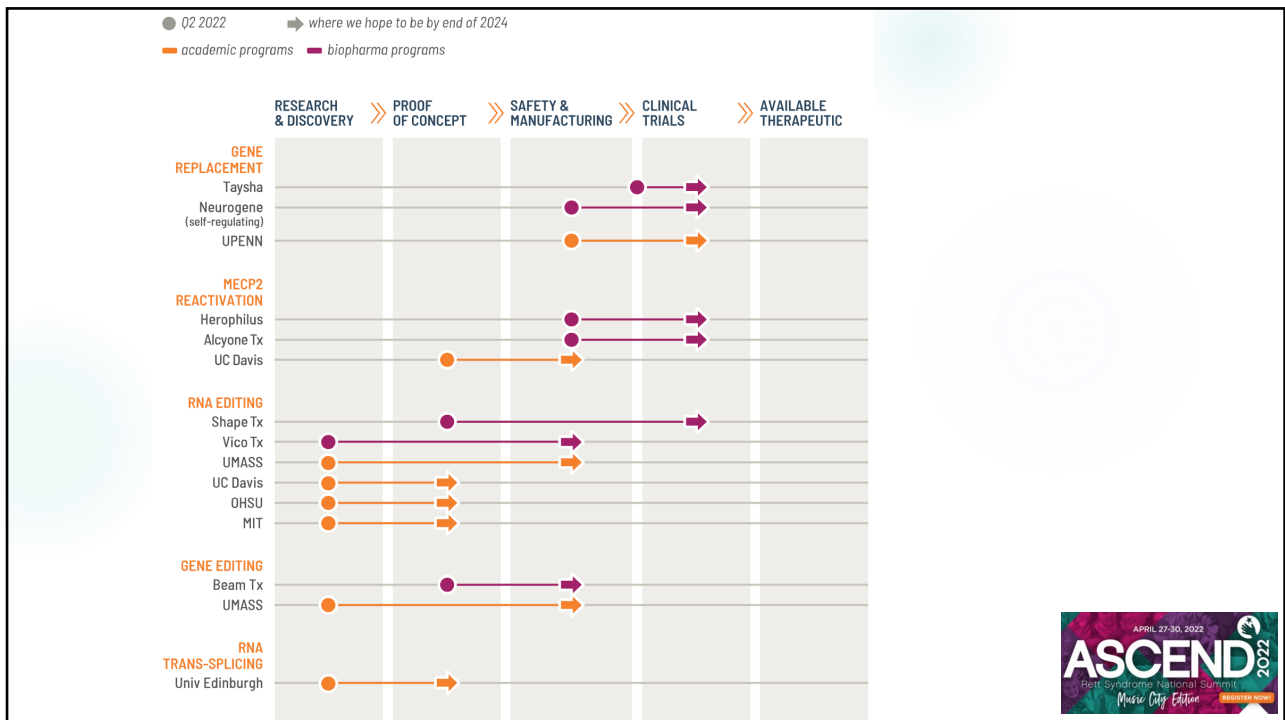


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Wege zum Ziel



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1. Gen Therapie

TAYSHA
GENE THERAPIES

TSHA-102

TSHA-102 is being developed for the treatment of Rett syndrome, one of the most common genetic causes of severe intellectual disability. TSHA-102 is constructed from a neuronal specific promoter, MeP426, coupled with the miniMECP2 transgene, a truncated version of MECP2, and miRNA-Responsive Auto-Regulatory Element, or miRARE, our novel miRNA target panel, packaged in self-complementary AAV9.



TAYSHA
GENE THERAPIES

03-29-2022

TAYSHA GENE THERAPIES ANNOUNCES INITIATION OF CLINICAL DEVELOPMENT OF TSHA-102 IN RETT SYNDROME

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Der Weg ...



1992

Adrian Bird, PhD,
discovers the
MECP2 gene



1999

Huda Zoghbi, PhD, discovers
MECP2 mutations cause Rett



2007

Adrian Bird discovers
Rett is reversible in mice



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3 Gründe für Optimismus



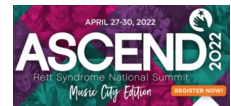
1. Single target: MECP2



2. Brain cells don't die



3. Boosting MECP2 reverses symptoms in mice



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Was wissen wir ... **REPORT** Reversal of Neurological Defects in a Mouse Model of Rett Syndrome

Jacky Guy¹, Jian Gan², Jim Selfridge¹, Stuart Cobb², Adrian Bird^{1,*}

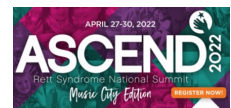
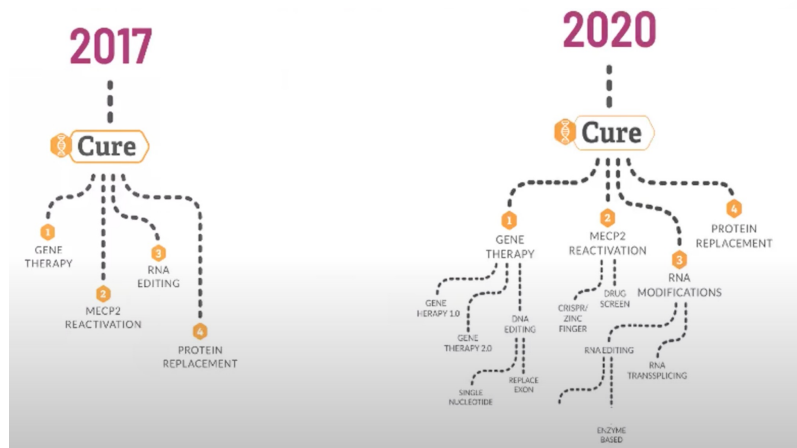
+ See all authors and affiliations

Science 23 Feb 2007:
Vol. 315, Issue 5815, pp. 1143-1147
DOI: 10.1126/science.1138389



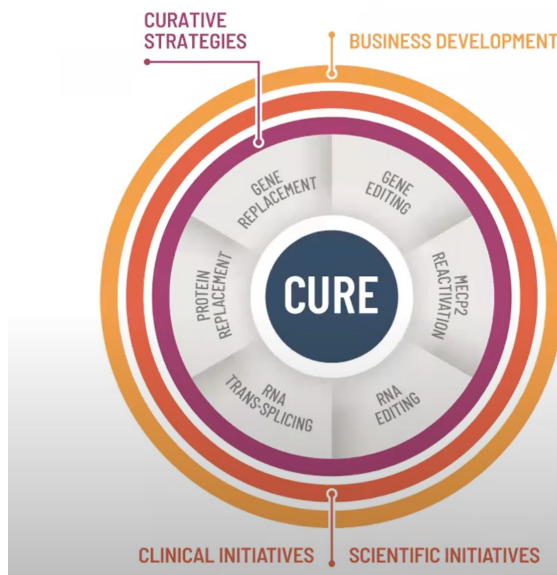
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Roadmap - Fahrplan



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CURE360



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Voraussetzungen für Studien

- Rett Syndrome Global Registry
- Digital natural history study
- Outcome measures
- Biomarkers
- Biorepository

BIOSENSORS

- Objective measures
- Measure something directly in the patient
- Continuous wear in the home
- New avenues

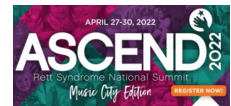


BIOMARKERS CAN PROVIDE AN EARLY SIGNAL OF DRUG EFFICACY

- **Molecular:** Changes at the cellular level that indicate the level of disease and can be measured in a tissue or biofluid
- **Biological:** Changes in a natural signal/pattern that can be measured through technology
- **Functional:** Changes in ability that can be measured through task-based action



Biomarkers allow us to determine target engagement and detect early signs of potential efficacy



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Wann CURE?

TO ANSWER THIS QUESTION WE NEED DATA FROM HUMAN CLINICAL TRIALS

- Is the treatment safe?
- Will there be symptom improvement in adults? If so, how much?
- Which symptoms improved?
- How well did AAV9 work?
- How well did intrathecal delivery work?



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Klinische Studien



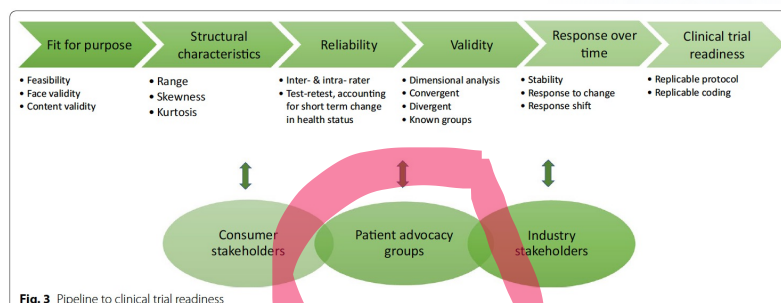
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Vorbereitungen ...

▶ Datebanken

▶ Register

...



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When Will We Have a Cure?



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Profiling the Early Phenotype of Rett Syndrome to Enhance
Awareness, Early Identification, and Targeted Intervention

Peter B Marschik
Sigrun Lang

Fulda, April 2022



Mitgliederversammlung Rett Deutschland
e.V., Prof. Dr. Dr. Peter Marschik

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- Meine Verbindung mit Ihnen ...

- **Vielschichtig**

- Privat
- **Beruflich**
- Forschungsauftrag
- Verbindend



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➤ **Woher ich komme und warum Göttingen**

- Meine Verbindung mit Ihnen ...

- **Vielschichtig**

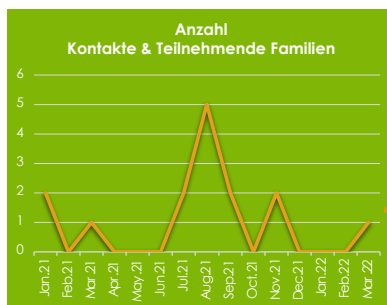
- **Privat**



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WIR brauchen IHRE UNTERSTÜTZUNG!!!

WIR brauchen viele viele viele VIDEOS der ersten 2 Lebensjahre



Ziel: > 80 Teilnehmende Familien



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pro rare austria
allianz für seltene erkrankungen

 Bundesministerium
Arbeit, Soziales, Gesundheit
und Konsumentenschutz



European
Reference
Networks

#ERNcare4Ua
Rare Diseases Doctors

**Nationaler Aktionsplan
für seltene Erkrankungen**

Undiagnosed Disease Program

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