### Rare diseases

<table>
<thead>
<tr>
<th>Page</th>
<th>Section</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Editorial Rare diseases: a challenge for medicine and public health</td>
</tr>
<tr>
<td>7</td>
<td>Focus Rare diseases in Germany – Developments in the status of medical care</td>
</tr>
<tr>
<td>17</td>
<td>Fact sheet Research on Rare Diseases in Germany – The cancer predisposition syndrome registry</td>
</tr>
<tr>
<td>24</td>
<td>Fact sheet Research on Rare Diseases in Germany – The GAIN Registry: a registry for individuals with congenital multi-organ autoimmune diseases</td>
</tr>
<tr>
<td>31</td>
<td>Fact sheet Research on Rare Diseases in Germany – Using small fish and super-resolution microscopy to track down a rare disease</td>
</tr>
</tbody>
</table>
Rare diseases: a challenge for medicine and public health

This issue of the Journal of Health Monitoring is dedicated to a public health topic for which population-wide health monitoring can hardly provide any data: rare diseases, their research and the care of those affected.

Rare diseases are also referred to as ‘orphan diseases’ and their medications as ‘orphan drugs’. These terms are used by those affected and researchers to describe the fact that they are orphans who have received little attention in research and healthcare. The prevalence of the individual, approximately 8,000 known rare diseases may be low, but the total population of those affected is not. In the European Union there are approximately 30 million people living with a rare disease; in Germany there are an estimated 4 million. Worldwide, it is estimated that 300 million people are affected [1].

Rare diseases are predominantly diseases of genetic origin with often severe, chronic courses. There are no diagnostic procedures or therapeutic guidelines for many rare diseases, and available treatments often only alleviate symptoms but cannot cure the disease. In a 2005 survey of 5,980 patients, the European Organisation for Rare Diseases (EURORDIS) found that 25% had waited between 5 and 30 years for a correct diagnosis, 40% of respondents had been misdiagnosed at the onset of the disease, which led to incorrect medication in 33%, surgery due to misdiagnosis in 16% and inappropriate psychological counselling in 10% [2, 3]. As a result, there is a lack of comprehensive expertise and seamless patient pathways.

The development of drugs for rare diseases also entails particular challenges. The pharmaceutical industry expects high costs but low revenues due to small case numbers. The ‘orphaning’ of drug development for rare diseases can be traced back to regulatory progress: as a result of the thalidomide tragedy, legislative changes were passed in the USA in 1962, according to which controlled studies must be carried out to prove the safety and efficacy of all drugs. Drug safety increased, while costs rose at the same time. Research and development of drugs for a small number of patients was postponed in favour of drugs for common diseases [4]. In the 1970s, patients with rare diseases in the USA joined forces, demanded the right to equal medical care and treatment and called for political action. Their commitment led to the passing of the first legislation for drugs for rare diseases, the U.S. Orphan Drug Act of 1983, which primarily contained financial incentives for the pharmaceutical industry. For the first time in the USA, this law defined rare diseases by their frequency (maximum 7 in 10,000 people). Laws with similar incentives but slightly different prevalence rates followed (Japan 1997: 4/10,000; Australia 1998: 1.1/10,000; EU 2000: 5/10,000) [5]. Recent studies identified orphan drug regulations in 92 out of 200 countries or regions analysed [6].

The heterogeneity of rare diseases, which encompass all medical disciplines, has long pushed rarity into the background as a common denominator and as the cause of the particular infrastructural problems [7]. This affects both research and the challenges in healthcare provision.
In their article, Schlangen and Heuing provide an overview of developments in the healthcare situation for rare diseases in Germany and describe goals, successes, and challenges. The National Action League for People with Rare Diseases (NAMSE), which was founded in 2010 on the initiative of the Federal Ministry of Health (BMG), the Federal Ministry of Education and Research (BMBF), the Alliance for Chronic Rare Diseases (ACHSE), a network of self-help organisations for people with rare diseases, and 25 other alliance partners, plays an important role in this. In 2013, NAMSE published a National Plan of Action for People with Rare Diseases. According to a report published in 2023 [8], establishing centres for rare diseases at three different levels (reference centres, centres of expertise and cooperating centres for a specific rare disease) as part of the action plan has already brought about significant improvements in healthcare.

A mapping of research into rare diseases from 2014 [9] shows that most of the projects were funded by the German Research Foundation (DFG) and the BMBF. Two thirds of the projects concerned disease-orientated basic research. In particular, rare oncological and haematological diseases were researched, another research area was rare genetic diseases, especially neurological diseases [9]. Since 2003, the BMBF has been funding networks that jointly research the causes and therapeutic approaches for rare diseases at various university locations. The patient registers often included in these networks provide the necessary data for clinical and healthcare research. Three research projects presented in this issue are examples of how complex the topic of rare diseases is and how important innovation and interdisciplinary and multinational cooperation are. Dutzmann et al. present the internationally networked cancer predisposition syndrome registry for the prevention and early detection of genetic alterations associated with an increased risk of cancer. Stapornwongkul et al. report on the GAIN registry (German genetic multi-organ Auto-Immunity Network), which records people with multi-organ autoimmune diseases in Germany, Italy and Portugal on the basis of a platform provided by the European Society for Immunodeficiencies (ESID). Endlich’s contribution describes a research project on a rare kidney disease (FSGS): this utilises a Nobel Prize-winning microscopy technique for the quantitative analysis of kidney tissue as well as high-throughput screening using zebrafish larvae for the rapid identification of potentially suitable drugs for treatment.

International research cooperation and sustainable funding are key to improving the diagnosis and treatment of rare diseases, especially in low- and middle-income countries. In 2019, Rare Disease International (RDI) signed a Memorandum of Understanding with the WHO and founded the Global Network for Rare Diseases (GNRD), based on the United Nations Declaration on Universal Health Coverage. The International Rare Diseases Research Consortium (IRDiRC) aims to ensure that all patients affected by a known rare disease receive the correct diagnosis within one year by 2027. European cooperation on rare diseases takes place, for example, in the European Joint Programme on Rare Diseases (EJP RD).

This issue of the Journal of Health Monitoring cannot cover the entire spectrum of topics relating to rare diseases, but aims to provide an insight into the many challenges and the special efforts being made to alleviate the suffering of many people with rare diseases.
Rare diseases: a challenge for medicine and public health

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Rare diseases in Germany – Developments in the status of medical care

Abstract

Background: Rare diseases are a heterogeneous group of complex clinical patterns, which more often than not run a chronic course. The fact that they are rare complicates the provision of medical care for the specific diseases.

Results: In the field of action titled ‘Care, Centres, Networks’ of its National Action Plan, the National Action League for People with Rare Diseases recommends the formation of a three-level, interconnected centre model. This form of care was investigated in two large research projects. It was shown that the time to diagnosis was markedly reduced. Commissioned by the Federal Ministry of Health, the expert report on the health status of people with rare diseases in Germany issued in 2023 concludes that the medical care provided to this group of people has improved markedly since the National Action Plan was introduced. The establishment of the Centres for Rare Diseases (ZSE, Zentren für Seltene Erkrankungen) is seen as the most important development. However, it is noted that there is still a lack of coordinated care provision pathways for referring patients to the appropriate facilities.

Conclusion: The provision of care to people with rare diseases has improved upon the implementation of the measures from the National Action Plan. In a next step, care provision pathways must be established across sector boundaries. Challenges remain in the area of psychosocial care and the long-term securing of funding for these structures.

1. Introduction

In the European Union (EU), a disease is considered rare if it afflicts no more than 5 in 10,000 people. According to estimates, roughly four million people with a rare disease live just in Germany [1], and some 30 million people are thought to be afflicted in the entire EU. Rare diseases form a group of very different and, in most cases, complex clinical patterns. Most rare diseases run a chronic course and are associated with restricted health and/or a limited life expectancy as they often lead to symptoms becoming manifest as early as in childhood. Some 80% of rare diseases are genetically determined or co-determined, and they are rarely curable.

Rare diseases have some special characteristics that render both care and research more difficult: even though there are many of them when added up, the number of people afflicted by a particular rare disease is low. Also, there are usually only a few experts available who can provide care to people with the respective rare disease and...
Rare diseases in Germany – Developments in the status of medical care

conduct research on the disease. Quality-assured care structures are therefore rare. People with rare diseases often go through years of an odyssey through the health care system – at least five years on average – before a definitive diagnosis is made, and this despite the fact that there has been rapid progress in diagnostic capabilities in recent years. Often, this means that therapeutic measures can be initiated only rather late, and diagnosis may come too late for some of the afflicted. To date, there are no firmly established structures in the German health care system that enable a specific diagnostic work-up and treatment by the respective experts. Often, there is no drug treatment available for rare diseases, mainly due to a lack of incentives for research and development.

In 2009, the Council of the European Union called on all member states to define and implement a strategy for improvement of the health scenario of people with rare diseases by the end of 2013 [2]. At the same time, the German Federal Ministry of Health (BMG) published a research report on the health care status of people with rare diseases in Germany and described prioritised fields of action as well as proposals for improvement and solution scenarios on the basis of scientific analyses [3].

Subsequently, the National Action League for People with Rare Diseases (NAMSE) was founded in 2010 based on the joint initiative of the Federal Ministry of Health (BMG), Federal Ministry of Education and Research (BMBF) and Alliance of Chronic Rare Diseases (ACHSE e.V.), as well as 25 other alliance partners – all of them central and umbrella organisations of the major stakeholders in the health care system. Today, the League works in two working groups and four topic-specific sub-working groups; selected work results are discussed and approved by the steering group (for the work of NAMSE, see Figure 1).

In 2013, the League published a National Action Plan for People with Rare Diseases, in which a total of 52 measures in six fields of action were proposed to improve the health status of people with rare diseases. Chapter 3.1, field of action ‘Care, Centres, Networks’, is dedicated to the topic of care [4]. It proposes a three-tier centre model with three types of centres which do not differ in terms of the quality of care, but in the range of services offered. The three working levels are envisioned to be interconnected to each other. The implementation of the proposed measures is monitored and documented by the NAMSE office and was scient-

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**Infobox 1**

**Rare diseases**

A total of about 30,000 diseases are known worldwide, of which some 8,000 are rare diseases, also called ‘orphan diseases’. For example, children afflicted by Hutchinson-Gilford syndrome, also known as progeria, appear to age as if at a time-lapse pace. Only a few cases of the disease are known in Germany. The metabolic disease cystic fibrosis (CF) affects more than 8,000 people in Germany and is also a rare disease. The European database for rare diseases, Orphanet (www.orpha.net), provides information on numerous rare diseases and medicines. The Care Atlas for Rare Diseases (se-atlas, www.se-atlas.de) provides an overview of care options for rare diseases in Germany. Information on rare diseases and patient associations is made available by an umbrella organisation called Alliance for Chronic Rare Diseases (ACHSE, www.achse-online.de).
Type B centres, specialist centres for a specific disease or group of diseases, also work on an outpatient and inpatient basis, but are in charge of the provision of care to people with a confirmed diagnosis or a solidly suspected diagnosis, e.g. a centre for rare neurological diseases. These disease-specific centres of expertise form the building block of the European Reference Networks (ERNs) required by Directive (2011/24/EU) [2] on the application of patients’ rights in cross-border health care. Type C centres provide disease or disease group-specific outpatient care in an interdisciplinary and multiprofessional setting.

2. Developments in the provision of care to people with rare diseases

Care centres for rare diseases

NAMSE recommended the introduction of an interconnected centre model in the ‘Care, Centres, Networks’ field of action of the National Action Plan [7]. This is based on three interconnected levels, which are structured according to the division of labour and which should not differ in terms of the quality of the care they provide, but in the range of services they offer. This centre model is designed to promote cooperation between the respective specialists as well as the sharing of expertise in the field of rare diseases on both a national and an international level. This is intended to establish the prerequisites for the provision of care close to home (Figure 2). Above all, the latter is also a demand of the patient self-help groups.

The type A centres, reference centres for rare diseases, are in charge of both inpatient and outpatient care and are the point of contact for patients with an unclear diagnosis. They have guides and capabilities for interdisciplinary case conferences and innovative special diagnostics.
A type C centre is primarily in charge of providing specific care services to patients with a confirmed diagnosis or a clear suspected diagnosis. The implementation of this network model is the central requirement at the heart of the National Action Plan of 2013. NAMSE has formulated quality criteria for structures and processes in the centres, which have been applied since 2021 through the involvement of an independent certification body within the framework of a certification procedure for type A centres [8]. A certification procedure for type B centres is in preparation.

More than 30 centres for rare diseases have been established at university hospitals in Germany in recent years (for an overview, see www.se-atlas.de). Some of the facilities have already successfully completed the certification procedure. They demonstrated that they meet the quality criteria formulated by NAMSE. The certification procedure is designed to promote transparency of the care scenario for patients, relatives and physicians in private practice.

Although specialised centres have been established according to these criteria in recent years, an online survey conducted for the 2023 report on the health status of people with rare diseases indicates that those afflicted are not yet sufficiently aware of these structures (Figure 3).

Testing new care approaches: Innovation Fund Projects TRANSLATE-NAMSE and ZSE-DUO

The TRANSLATE-NAMSE project was funded from 2017 to 2020 in the framework of the Innovation Fund at the Federal Joint Committee (G-BA) aiming to introduce and solidly implement the centre structures and processes proposed by NAMSE. Guides and medical coordinators, an essential element of the structural quality of a NAMSE type A centre, were recruited at all participating sites as part of the project. A total of ten university hospitals with outstanding clinical expertise were involved and were linked within the framework of process quality. Some of the centres in this network also took on innovative special diagnostics. Interdisciplinary case conferences were the main building block and a new service in the context of which the need for this diagnostic work-up was affirmed. The new forms of care tested in the project significantly shortened the diagnostic process and significantly improved the efficiency of the care provided. For example, the diagnostic process for patients without a confirmed diagnosis took just half a year, while children had previously been treated for their symptoms in various care facilities for an average of four years and adults for eight.

Still, it became clear that there is still a low level of awareness of the existence of the care services offered by type A Centres among primary care providers and patients [9].
The ZSE-DUO project (Dual guide structure for clarifying unclear diagnoses in centres for rare diseases) [10], funded by the Innovation Fund, also proposes suitable disease-transcending structures and processes in order to identify diagnoses for people with unclear diagnoses and suspected rare diseases. Here, a dual guide contact point was created that involves not only a somatic specialist, but also psychiatric-psychosomatic expertise. This is intended to reduce the time to diagnosis and care offers are to be made available to the patients more readily and efficiently. As such, the project addresses the need for psychological support, which was once again highlighted in the current report of the Fraunhofer Institute for Systems and Innovation Research IS [6], although access to and the ensuing utilisation of psychosocial care services is still considered to be rather difficult by some of the stakeholders surveyed in the report. The lack of psychotherapists is seen as the root cause in this regard. Self-help continues to play a major role in the support for patients at this point, in that it facilitates discussion offers of a peer-to-peer type of sharing and by providing knowledge and information that is made comprehensible for laypersons. Patient self-help plays an important role specifically in the field of rare diseases, because patients and their relatives are actually the experts for the respective disease and are therefore important partners for those attending to them.

The Alliance for Chronic Rare Diseases – or ACHSE for short – is the umbrella organisation of and for people with chronic rare diseases and their relatives in Germany. Comprising 130 patient organisations, ACHSE pools the existing expertise and knowledge in the field of rare diseases and represents the interests of the afflicted people.

Legislation for better care for rare diseases

Some ten years after publication of the National Action Plan, NAMSE has initiated important improvements in the field of care [11]. The Federal Joint Committee (G-BA) defined the special tasks of centres for rare diseases and established nationwide quality requirements for the first time at the end of 2019 in the Act to Strengthen Nursing Staff (Nursing Staff Strengthening Act), §136c section 5 of the Fifth Social Code (SGB V) [12]. This was taking into account the requirements for centres previously defined by NAMSE. These special tasks are to be financed through centre surcharges. This is the prerequisite for a sustainable implementation of the centre model.

With the 2015 Patient Data Protection Act (PDSG), a semantics centre was established at the Federal Institute for Drugs and Medical Devices (BfArM), and the Digital Care and Nursing Modernisation Act (DVPMG) of 3 June 2021 established the basis for specification of the unique coding of rare diseases in inpatient settings. Implementation has been mandatory since 1 January 2023. An important milestone has been reached through the mandatory, precise coding of rare diseases. Coding makes rare diseases visible. The precise, digitally evaluable designation of the diagnosis is also relevant not only for billing purposes, but also in particular for epidemiology, research and the application of artificial intelligence (AI). It is also of elementary importance for patient safety, so that in the clinical context – including, and especially, in emergencies – special risk factors and therapeutic needs can be taken into account immediately [13].

Many other projects and (legal) initiatives have been initiated in recent years and contribute to the improvements
Rare diseases in Germany – Developments in the status of medical care

The expert report on the health status of people with rare diseases [6], commissioned by the BMG and published in 2023, states that the care status of people with rare diseases has improved compared to 2009 and to the introduction and implementation of the National Action Plan (NAP) in 2012. In particular, the establishment of a specialised and interconnected care structure through the development and establishment of the recommended centre in the current care scenario. For an overview of selected projects and initiatives, see Table 1.

3. Discussion and conclusion

Many important milestones in the provision of care have been achieved since the National Action League for People with Rare Diseases was founded in 2010.

Table 1
Expert opinions, recommendations and projects related to rare diseases
Source: own illustration

<table>
<thead>
<tr>
<th>Study</th>
<th>Topic/goals</th>
<th>Time</th>
<th>Source</th>
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<tbody>
<tr>
<td>Study on the health status of people with rare diseases</td>
<td>Measures to improve the health status of people afflicted by rare diseases</td>
<td>2009</td>
<td>[3]</td>
</tr>
<tr>
<td>EU Recommendation for Action in the Field of Rare Diseases</td>
<td>Recommendation on diagnosis, treatment and care for people afflicted by rare diseases</td>
<td>2009</td>
<td>[2]</td>
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<tr>
<td>National Action Plan for People with Rare Diseases</td>
<td></td>
<td>2010</td>
<td>[7]</td>
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<tr>
<td>Research</td>
<td></td>
<td></td>
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<tr>
<td>NARSE – National Registry for Rare Diseases</td>
<td>Establishment of a national registry for rare diseases</td>
<td>since 2021</td>
<td>[14]</td>
</tr>
<tr>
<td>FAIR4Rare</td>
<td>Accompanying evaluation of the set-up process of an open National Registry for Rare Diseases (NARSE)</td>
<td>2023–2025</td>
<td>[15]</td>
</tr>
<tr>
<td>ESE-Best</td>
<td>Evaluation of interface management concepts for rare diseases</td>
<td>2019–2022</td>
<td>[16]</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>se-atlas</td>
<td>Care atlas for people with rare diseases</td>
<td>since 2015</td>
<td>[17]</td>
</tr>
<tr>
<td>Centre surcharges</td>
<td>Hospitals acting as centres that perform special inpatient tasks can receive financial surcharges for this purpose</td>
<td>2019</td>
<td>[12]</td>
</tr>
<tr>
<td>Certification procedure for centres for rare diseases</td>
<td>Certification by independent certification body clarcert GmbH</td>
<td>2021</td>
<td>[8]</td>
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</table>

Research projects supported by the Innovation Fund demonstrate the effectiveness of the structure comprising three types of care centres.
Rare diseases in Germany – Developments in the status of medical care

Thus, many afflicted persons are (still) dependent on off-label use, i.e. the use of a drug outside its areas of application as approved by the regulatory authorities. However, there is no indication from the interviews of any problems occurring particularly frequently in this regard.

The uniform and unambiguous coding in the inpatient setting by means of Alpha-ID-SE, which will become mandatory on 1 January 2023, will for the first time enable unambiguous recording and thus better visibility of rare diseases for the purposes of rare disease research and care. The National Registry for Rare Diseases (NARSE) [14] initiated by the Eva Luise and Horst Köhler Foundation is designed to systematically record especially very rare diseases in order to improve the respective care in the future. The effectiveness of this registry is to be tested within the framework of the FAIR4Rare innovation fund project [15].

Improvements, especially in the diagnosis of rare diseases, might also be on the horizon due to the use of artificial intelligence, although there are still many open questions to be discussed and answered [6]. Undoubtedly, the various projects and political undertakings set up important prerequisites in recent years with regard to the harmonisation of data, their consolidation and use, which form an important basis for the application of AI.

According to the above-mentioned expert report, challenges exist in the connection of the centres in particular to SHI-accredited medical care [6]. Although the introduction of the medical care atlas for rare diseases (se-atlas) in 2015 established an overview of the existing care structures, these still seem to be known only to an insufficient extent by the primary care providers. According to the expert opinion, a good and low-threshold offer is available according
Rare diseases in Germany – Developments in the status of medical care

to the centres’ point of view, which, however, obviously does not reach the target group. Whether or not the afflicted receive a specific diagnosis and ensuing treatment or continue to go through an odyssey still seems to depend largely on coincidence and their individual commitment. The BMG-funded project ‘Evaluation of interface management concepts for rare diseases: systematic stocktaking & development of best practice recommendations (ESE-best)’ [16] from 2022 also concluded that the care landscape has changed for the better through the introduction of the centre model, but that this specialised care is characterised in particular by interface problems that can significantly impair the quality of care. Among other things, deficits in communication and information transfer between the sectors and organisational deficits are mentioned here. The project has formulated recommendations for the management of interfaces. The BMG has commissioned the NAMSE office to work towards implementation of the recommendations in health care practice. The NAMSE working groups will address these topics in 2023 to 2026 and develop proposals for solutions.

In conclusion, it can be said that effective building blocks for improving the care provided to people with rare diseases have been developed since the National Action Plan was published in 2013, and must now be linked together in order to achieve an improvement in care as the dedicated goal of the initiative. The fact that people with more common diseases also benefit from further development of health care for rare diseases is also emphasised in the conclusion of the report: ‘Rare diseases are some sort of ‘burning lens’, as it were, for the German health and social care system and allow fundamental challenges and needs for further development to come to the fore at an early stage. As such, rare diseases are an important opportunity allowing us to draw lessons for further development of the health care system and for identification of best-practice approaches from which the provision of care could benefit across the board. Accordingly, rare diseases can help to ensure that all people, regardless of the prevalence of their individual condition, receive good, needs-based health care and are enabled to participate in society.’ [6, p. 64]

There is a need to implement structured patient pathways to further develop the provision of care.
Rare diseases in Germany – Developments in the status of medical care

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Research on Rare Diseases in Germany – The cancer predisposition syndrome registry

Abstract
Background: Cancer predisposition syndromes (CPS) are rare diseases that are associated with an increased risk of cancer due to genetic alterations. At least 8% of all cases of childhood cancer are attributable to CPS [1, 2]. The CPS registry was launched in 2017 to learn more about CPS and to improve the care to those afflicted by these diseases.

Methods: This is an internationally networked registry with associated accompanying studies that investigate cancer risks and spectra, the possibilities of cancer prevention, early detection and therapy.

Results: For several of these syndromes, new insights into the cancer risks and cancer types as well as factors modifying cancer risk have been gained. In addition, experimental, psycho-oncological, preclinical and clinical studies were initiated.

Conclusions: The CPS registry is an example of how progress can be made within a short period of time to the benefit of individuals with rare diseases through systematic data collection and research.

Introduction
Cancer predisposition syndromes (CPS) are rare genetic diseases that are associated with an increased risk of cancer compared to healthy individuals. In both children and adults, CPS are among the most important risk factors for cancer and at least 8% [1, 2] of people with cancer suffer from a CPS. One of the better-known CPS is Li-Fraumeni Syndrome (LFS) with 16,000 afflicted individuals in Germany with a prevalence of 1:5,000 [3]. LFS is associated with a drastically increased risk of a variety of cancers in both childhood and adulthood. Various questions arise for each of the many different CPS: How high is the cancer risk in different phases of life? What types of cancer occur? Which genetic and environmental factors influence the cancer risk of the afflicted? How can the cancer risk of the afflicted be reduced? How can cancer be recognised early in the afflicted? What are the special features of cancer treatment? What are the psycho-oncological consequences and needs?

In order to address these questions, the CPS registry (www.krebs-praedisposition.de) was started in 2017. Research for people with CPS benefits not only people with CPS, but also individuals with sporadic, i.e. non-hereditary, types of cancer, as hereditary and sporadic cancers are
Infobox
Translational Research on Rare Diseases – a funding priority of the Federal Ministry of Education and Research

A disease is considered rare if fewer than five in 10,000 people are affected by such a diagnosis. More than 8,000 rare diseases are known. It is estimated that more than four million people in Germany alone are affected by a rare disease. Around 80% of rare diseases are genetically determined, some diseases cause their first symptoms in childhood. However, the causes of the disease are often unexplored. The relatively small number of people affected, experts and suitable medicines complicate the path to a diagnosis and appropriate therapy. If there is no diagnosis or it can only be made at a late stage, irreversible courses of the disease are often a result. Therefore, research is vital for those affected. Basic research plays an important role here: it not only provides new insights into rare diseases, but can also contribute to a better understanding of more common diseases.

Since 2003, the Federal Ministry of Education and Research (BMBF) has been funding networks that jointly research causes and therapeutic approaches for rare diseases at various university locations. A coordination office supports these networks, among other things, in presenting their results to the public (see also https://www.research4rare.de/wp-content/uploads/2023/05/Poster_R4R_engl_2019-2026.pdf). At the European level, the research consortia are involved in the European Reference Networks (ERN) on rare diseases. In addition, there are international programmes, such as the European Joint Programme on Rare Diseases (EJP RD) for research into the diagnosis and therapy of rare diseases, in which the BMBF also participates.

Research on Rare Diseases in Germany – The cancer predisposition syndrome registry

based on identical signalling pathways. For example, Li-Fraumeni Syndrome is caused by hereditary variants in \( TP53 \), a gene that is also altered in many sporadic types of cancer. CPS research is therefore of great importance for cancer research in general.

Project

The CPS registry was opened in 2017 as a non-interventional observational study with the primary aim of addressing the questions mentioned above. The focus of data collection is on genetic findings, detailed information on cancer in patients and their relatives as well as early detection measures. A biobank and an MRI image database are an integral part of the registry. The CPS registry serves as the basis for the ADDRess (Translational Research for Persons with Abnormal DNA Damage Response) research network, which focuses explicitly on the CPS subgroup of DNA repair defects associated with a particularly high cancer risk. This national consortium addresses various issues relating to the causes of CPS, psycho-oncology, surveillance by MRI and/or liquid biopsy (detection of cell-free tumour DNA via a blood sample), mechanisms of carcinogenesis and novel treatments.

The aim of the registry is to create research structures, particularly for patients, which are not covered by the existing activities of other research groups, such as in the areas of familial breast and ovarian cancer and hereditary colon cancer. There is also a close exchange with the established therapy studies in the field of paediatric oncology. The registry is open to patients of all ages and with all types of CPS. Inclusion in the registry is possible either via an attending centre, which is the case especially in the field of paediatric oncology, or by the patients themselves as self-registration by contacting the CPS registry directly and can be done by both German and international patients. Furthermore, an independent CPS

Results and classification

After the registry was opened in 2017 in collaboration with the Department of Paediatric Haematology and Oncology of Hannover Medical School and the Hopp Children’s Cancer Center Heidelberg, 923 patients were registered by July 2023 (Figure 1). Each year, there are some 150 new entries, with an upward trend. The registry is open to patients of all ages and with all types of CPS. Inclusion in the registry is possible either via an attending centre, which is the case especially in the field of paediatric oncology, or by the patients themselves as self-registration by contacting the CPS registry directly and can be done by both German and international patients. Furthermore, an independent CPS

Figure 1
Cumulative registrations in the CPS registry
Source: CPS Registry, as of: 31 July 2023

Number of patients

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>2017</td>
<td>100</td>
</tr>
<tr>
<td>2018</td>
<td>200</td>
</tr>
<tr>
<td>2019</td>
<td>300</td>
</tr>
<tr>
<td>2020</td>
<td>400</td>
</tr>
<tr>
<td>2021</td>
<td>500</td>
</tr>
<tr>
<td>2022</td>
<td>600</td>
</tr>
<tr>
<td>2023</td>
<td>700</td>
</tr>
</tbody>
</table>
outpatient clinic has been established at the Department of Paediatric Haematology and Oncology at Hannover Medical School, where patients with CPS can receive counselling and treatment. It is also possible to carry out early cancer detection screening there, especially for people with LFS and for children and adolescents with diverse CPS. The close spatial, personnel and organisational cooperation between the CPS outpatient clinic and the CPS registry enables not only the recruitment of numerous patients for the registry, but also enhances the expertise of the attending physicians based on the knowledge gained from the registry activities. The increasing registration numbers (Figure 1) offer the opportunity to carry out meaningful analyses of the data and to better understand various types of CPS. Individuals afflicted by various CPS can benefit directly from these insights and their implementation in clinical settings, for example by adapting the early detection of cancer. Inclusion in the CPS register is by no means a prerequisite for connection to the CPS outpatient clinic, though. In addition, afflicted individuals often become aware of the activities of the CPS register via social networks and patient organisations. In addition, the website www.krebs-praedisposition.de has been set up, which offers a wealth of information on many different CPS for both healthcare professionals and patients in addition to the online representation of the CPS Registry. In addition to data collection, professional, individualised counselling for patients with CPS is another important aspect of the work in the registry. This takes place either by telephone via the CPS registry physicians or during a personal appointment by the CPS outpatient physicians in the above-mentioned CPS outpatient clinic at Hannover Medical School, where appointments for patients from all over Germany are made. Through its sub-projects and close cooperation with the CPS outpatient clinic, the registry combines research, clinical counselling and early cancer detection, so that the knowledge thus gained can lead to significant improvements in the care provided to people with CPS.

The results obtained to date include two population-based epidemiological studies in which the risk of cancer in childhood was calculated for various CPS [4, 5]. This was done for patients with Fanconi anaemia (FA), ataxia telangiectasia (AT) and the Beckwith-Wiedemann spectrum (BWSp) through a comparison to data from the German Childhood Cancer Registry, in which almost all cases of childhood cancer are registered. The risk of developing cancer by the age of 18 was found to be 39 times higher in children with FA and 56 times higher in children with AT (as compared to the general population of the same age). Children with BWSp had a 32-fold increased risk of developing cancer by the age of 15. In addition, the cancer spectrum for the aforementioned diseases and subgroups thereof in childhood was determined. This work has important implications for risk-adapted early detection, which are already being implemented clinically. For example, certain examinations may be started at a later age or early detection measures may be intensified or relaxed for certain subgroups depending on the cancer risk. Specifically, this means, e.g., that the annual bone marrow puncture as part of early cancer detection in children with FA subgroups FA-A, FA-C or FA-G is not started until after the age of three, as the earliest occurrence of myelodysplastic syndrome or acute myeloid leukaemia was not observed at the age of four. In contrast, more comprehensive cancer screening is...
Cancer predisposition syndromes are therefore among the most important cancer risk factors in children and adults alike.

Research on Rare Diseases in Germany – The cancer predisposition syndrome registry

recommended for children with FA subgroups FA-D1 and FA-N as the cancer spectrum is different. An increased risk of cancer, particularly hepatoblastoma and nephroblastoma, has been observed in children with BWSp, which supports the recommended regular sonographic and clinical examinations. Patients with a ‘loss of methylation in imprinting centre 2 (IC2-LOM)’ are an exception, as these early detection examinations can be dispensed in this cohort due to the low risk of cancer.

Other studies [6, 7] looked at the spectrum of diseases associated with germline variants in TP53 or Li-Fraumeni Syndrome (LFS), one of the most important CPS. It was shown that different clinical manifestations and courses can occur within LFS. The spectrum was used to reveal clinically relevant genotype-phenotype correlations, showing that different genetic changes within a gene can, for example, lead to different types of cancer and different ages at onset. This may be important for risk-adapted early detection in the future.

Another study quantified the significance of adult CPS genes in childhood and adolescence for the first time [8]. Adult CPS genes are known to lead to an increased risk of cancer in adulthood. Examples include the BRCA1 and BRCA2 genes, which are associated with an increased risk of breast cancer. Variants in these genes already play a role in childhood and adolescence, but with low penetrance (the penetrance describes the extent to which a genetic change is clinically expressed). This work has important implications for genetic counselling, as such variants are increasingly being identified by panel sequencing, a method of comprehensive human genetic testing. Cancer screening is currently not recommended for healthy children and adolescents in whom one of these variants has been detected. However, the results of further studies showed that children and adolescents who have already experienced cancer and who have a pathogenic variant in an adult CPS gene may be at increased risk of developing a second cancer (second neoplasia), especially if they have undergone genotoxic therapy such as radiotherapy.

The CPS registry has already provided valuable insights for the provision of care to people with CPS. By continuing the CPS registry and the already established sub-projects ADDRess and Liquid Biopsy, further significant research results are to be obtained that will improve the early detection of cancer in people with CPS and optimise psychosocial support for afflicted patients and their families. In addition, further causes of CPS are to be identified and novel therapeutic approaches are to be generated. One important aspect of the CPS registry in conjunction with the CPS outpatient clinic is to offer patients a point of contact at which their rare disease is taken seriously and where they can get expert advice and optimal treatment.

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DOI 10.25646/11828
The German version of the article is available at: www.rki.de/jhealthmonitor

Data protection and ethics
The activities of the registry are carried out in strict compliance with the data protection provisions of the EU General Data Protection Regulation (GDPR) and the German Federal Data Protection Act (BDSG). The ethics committee of the Hannover Medical School has reviewed the registry and issued an approving vote with application number 7233. Each participant is being informed in detail about the study prior to participation and subsequently has to provide written consent to participation.

Data availability
We are in close cooperation within the framework of international collaborations. This enables us to generate sufficiently large study cohorts for the results to be significant, despite the fact that we are working in the field of rare diseases. If covered by the ethics vote and consent, the data collected by the CPS registry is made available within the framework of certain CPS research projects. In addition, registry subjects have the option of agreeing or declining to be contacted again for optional inclusion in follow-up or accompanying studies. This is done as part of the initial consent and can also be subsequently amended or withdrawn at any time.

The data used for research collaborations are used or passed on in anonymised form. Requests for data transfer can be directed to the CPS Registry Centre at the Clinic for Paediatric Haematology and Oncology at Hannover Medical School.

Funding
The CPS registry is funded by the German Childhood Cancer Foundation (Grant 2021.25). The ADDRess project is funded by the Federal Ministry of Education and Research (Grant 01GM2205A).

Conflicts of interest
The authors declared no conflicts of interest.

Acknowledgement
We wish to thank the afflicted individuals and cooperating doctors for their support of the research. We would also like to express our gratitude to the German Childhood Cancer Foundation and the BMBF.

References

Research on Rare Diseases in Germany – The GAIN Registry: a registry for individuals with congenital multi-organ autoimmune diseases

Abstract

Background: Patient registries are an important tool for networking medical caregivers and research, especially in the field of rare diseases. Individuals afflicted by multi-organ autoimmune diseases typically suffer from inflammation of multiple organs.

Project: GAIN (German genetic multi-organ Auto-Immunity Network) is the German network for research and therapy optimisation for individuals with congenital multi-organ autoimmune diseases. As a sub-project of the network, the registry systematically collects data from this patient group and makes it available for research purposes.

Results: A data set was developed and made available for the GAIN Registry that can map the complex clinical status of persons with multi-organ autoimmune diseases. Data from 486 individuals have been documented to date.

Conclusions: The GAIN register allows for a very comprehensive documentation that clearly goes beyond previous approaches, e.g. by linking it to biosamples collected in the consortium. The planned inclusion of patients in the documentation, e.g. data on quality of life, opens up a new field.

MULTI-ORGAN AUTOIMMUNE DISEASES · RARE DISEASES · QUALITY OF LIFE · CONGENITAL IMMUNODEFICIENCIES

Introduction

Congenital multi-organ autoimmune diseases belong to the extremely rare diseases. In multi-organ autoimmune diseases, the body’s immune system mistakenly attacks its own organs. Afflicted people typically experience inflammation in several organs, for example bone marrow, intestines, lungs, kidneys, skin and central nervous system. The complexity of the disease patterns and the insufficient data make it difficult to diagnose and treat the afflicted patients. Monogenic mutations (changes affecting one gene) in genes that regulate the immune system are already known to be a cause. However, the presence of a gene mutation alone does not determine whether the disease actually becomes manifest in a patient. In addition to other as of yet unknown gene mutations, environmental factors such as lifestyle and infections may also play a role in the development of multi-organ autoimmune disease. Research into these diseases may also contribute to the understanding and treatment of more common polygenic (affecting multiple genes) autoimmune diseases [1].
GAIN (German genetic multi-organ Auto-Immunity Network) is the German network for research and therapy optimisation for individuals with congenital multi-organ autoimmune diseases. The different sub-projects of the GAIN consortium aim to improve the understanding of the development of disease and treatment of individuals with such autoimmune diseases. The GAIN Registry is a central component in the consortium and promotes cooperation between the subprojects, which are described in detail on the GAIN website (www.g-a-i-n.de). These include a biobank coordinated by the Hannover Unified Biobank (HUB) with decentralised sample storage, which supports high-quality biospecimen collection from individuals registered in GAIN. Linking these valuable biospecimens with the associated data from the registry provides optimal support to the research projects in the GAIN consortium.

Patients with immunodeficiencies have been documented for roughly 20 years at the European level in the online registry of the European Society for Immunodeficiencies (ESID). In addition, a national online registry for people with primary (congenital) immunodeficiencies, the PID-NET Registry, was established in Germany starting in 2009. At the European level, the research consortia are involved in the European Reference Networks (ERN) on rare diseases. In addition, there are international programmes, such as the European Joint Programme on Rare Diseases (EJP RD) for research into the diagnosis and therapy of rare diseases, in which the BMBF also participates.

The GAIN Registry was implemented as a detailed (level 2) data set in the ESID Registry. It is thus available to all ESID centres (https://esid.org/Working-Parties/Registry-Working-Party/Documenting-centers) for documentation. The ESID Registry contains a core data set (level 1), which is also being documented for all GAIN patients. Individuals with a confirmed gene mutation known to cause a multi-organ autoimmune disease can be entered in the registry. However, individuals with multi-organ autoimmune diseases that have not yet been genetically defined can be included as well. All individuals must meet the criteria of the ESID Registry [4]. The decision concerning inclusion in the registry is at the discretion of the attending physician. Patients with an acquired immune deficiency are not included. The most important data source for the registry are the (electronic) patient records. Information originating from local research databases, e.g. on patients’ genetic information, is integrated as well. As a third source, information from questionnaires completed by the afflicted individuals is added to the registry, e.g. on the quality of life issue. No identifying data of the individuals is stored in the registry locally in the documenting centres and according to the rights of use. The documenting
centres are clinical institutions such as university hospitals at which the patients are treated. Medical documentalists of the centres transfer the information from the various sources to the registry. For information on data protection, please refer to the section ‘Data protection and ethics’.

Results and classification
A comprehensive dataset designed and implemented for the GAIN Registry makes it possible to map the complex clinical patterns of people with multi-organ autoimmune diseases. The data structure used is similar to that of an electronic patient record.

Information about afflicted persons that remains unchanged over time is only collected once. Information on laboratory and diagnostic findings as well as questionnaires can be documented repeatedly for each visit to the respective centre. It is aimed to have the included individuals visit and associated documentation in the registry made at least annually. Therapies, infections as well as diseases and other organ-related symptoms are also recorded. For this purpose, it is always possible to specify a start and completion in order to map the course over time. The structure of the GAIN data set can be viewed via a demo version of the ESID Registry (https://cci-esid-reg-demo-app.uniklinik-freiburg.de/EERS, User name: demouser, password: Demo-2019) [5].

To improve its interoperability and sustainability, the GAIN data set is based on international coding systems. This is an important prerequisite to enable comparison or merging with other datasets at a later point in time.

In the GAIN Registry, in addition to the IUIS classification [6] used as a standard in the ESID Registry, the main clinical diagnosis is recorded using the current International Classification of Diseases (ICD-11) of the World Health Organisation [7] and the so-called ORPHA nomenclature. The ORPHA nomenclature is maintained by the European Commission-funded ‘orphanet’ consortium and...
Research on Rare Diseases in Germany – The GAIN Registry

Table 1
Genes with mutations of those genetically tested in the GAIN Registry (N=421, n=217 women, n=204 men), sorted by incidence.†

<table>
<thead>
<tr>
<th>Genes with mutations</th>
<th>Number (N=421)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>NFkB1</td>
<td>57</td>
<td>13.5</td>
</tr>
<tr>
<td>CTLA4</td>
<td>41</td>
<td>9.7</td>
</tr>
<tr>
<td>TNFRSF13B</td>
<td>41</td>
<td>9.7</td>
</tr>
<tr>
<td>NFkB2</td>
<td>19</td>
<td>4.5</td>
</tr>
<tr>
<td>STAT3</td>
<td>18</td>
<td>4.3</td>
</tr>
<tr>
<td>STAT3 GOF (gain-of-function)</td>
<td>18</td>
<td>4.3</td>
</tr>
<tr>
<td>LRBA</td>
<td>13</td>
<td>3.1</td>
</tr>
<tr>
<td>ADA2</td>
<td>12</td>
<td>2.9</td>
</tr>
<tr>
<td>STAT1</td>
<td>10</td>
<td>2.4</td>
</tr>
<tr>
<td>PIK3CD</td>
<td>9</td>
<td>2.1</td>
</tr>
<tr>
<td>STAT1 GOF (gain-of-function)</td>
<td>8</td>
<td>1.9</td>
</tr>
<tr>
<td>IKZF1</td>
<td>7</td>
<td>1.7</td>
</tr>
<tr>
<td>ICOS</td>
<td>6</td>
<td>1.4</td>
</tr>
<tr>
<td>TNFAIP3</td>
<td>6</td>
<td>1.4</td>
</tr>
<tr>
<td>FAS</td>
<td>5</td>
<td>1.2</td>
</tr>
<tr>
<td>BACH2</td>
<td>4</td>
<td>1.0</td>
</tr>
<tr>
<td>CARMIL2</td>
<td>3</td>
<td>0.7</td>
</tr>
<tr>
<td>UNC13D</td>
<td>3</td>
<td>0.7</td>
</tr>
<tr>
<td>CARD11</td>
<td>2</td>
<td>0.5</td>
</tr>
<tr>
<td>FLG</td>
<td>2</td>
<td>0.5</td>
</tr>
<tr>
<td>MST1</td>
<td>2</td>
<td>0.5</td>
</tr>
<tr>
<td>PIK3R1</td>
<td>2</td>
<td>0.5</td>
</tr>
<tr>
<td>SH2D1A</td>
<td>2</td>
<td>0.5</td>
</tr>
<tr>
<td>Other genes</td>
<td>25</td>
<td>5.9</td>
</tr>
<tr>
<td>No mutation detected</td>
<td>106</td>
<td>25.2</td>
</tr>
<tr>
<td>Results pending</td>
<td>22</td>
<td>5.2</td>
</tr>
</tbody>
</table>

† Only genes documented in more than one individual are listed. There can be multiple mutated genes per each person, which is why the percentages do not add up to 100%.

The aim of the GAIN Registry is to achieve the best possible characterisation of those afflicted in order to gain insights into the incidence and course of the diseases, the course of therapy and disease-related restrictions on quality of life.

was developed specifically for rare diseases [8]. The Human Phenotype Ontology (HPO) was chosen for documentation of symptoms [9]. The catalogue is made available directly via an interface (https://hpo.jax.org/api/hpo/docs) in the GAIN Registry to assure that the most current status is always available. Drugs are coded according to their ingredients using the ATC code (Anatomical-Therapeutic-Chemical Classification) [10]. In addition, where possible, the full product name of the drug is documented using a table provided by the European Medicines Agency (EMA). The table contains all medicines approved in Europe [11].

Currently, twelve different centres document in the GAIN Registry, ten centres from various regions within Germany (Figure 1) and one centre each from Milan, Italy and Lisbon, Portugal.

Between 11 January 2021 and 15 May 2023, a total of 486 individuals were included in the GAIN Registry, 258 women (53.1 %) and 228 men (46.9 %). The average age is 39.5 years. If no information on the day or month of birth was available, the middle of the month (15th) or the middle of the year (1st July) was used for the calculation.

A total of 421 afflicted individuals (86.6 %) had a genetic test documented in the registry. At least one gene mutation was detected in 69.6 % (n=293) of those tested. In total, mutations in 45 different genes were documented. The gene most frequently affected (57 afflicted persons, 13.5 %) is the NFkB1 gene (Table 1) associated with common variable immunodeficiency (CVID). The group of patients with congenital mutations in this gene is the subject of a separate research project within the GAIN network.

Since 2023, the GAIN consortium has been supplemented by an epidemiological study on the quality of life of patients with multi-organ autoimmune diseases and how it relates to patient-oriented care (Qualy-GAIN). Here, the GAIN Registry is an important prerequisite for identifying subjects for the study. Furthermore, in upcoming years, the registry will provide the necessary infrastructure to directly capture not only the questionnaires already used...
Ten different centres in Germany and one centre each in Italy and Portugal are currently supplying documentation to the GAIN Registry.

Multi-organ autoimmune diseases can be caused by a mutation in one of many genes; the afflicted individuals in the GAIN Registry currently have mutations in 45 different genes.

in the GAIN consortium, but also PROMs (Patient Reported Outcome Measures) and PREMs (Patient Reported Experience Measures) related to the Qualy-GAIN study via an app. PROMs collect patient-reported treatment outcomes, e.g. regarding quality of life or health status, by means of standardised questionnaires. PREMs records patients’ experiences during the treatment process, e.g. with regard to care coordination or waiting times. This data will then be linked to the data already present in the registry.

Data protection and ethics
The registry is subject to the data protection regulations of the EU Data Protection Regulation (DSGVO) and the Federal Data Protection Act (BDSG) and complies strictly. The ESID Registry complies with the guidelines of the Declaration of Helsinki and has been approved by the Ethics Committee of the University of Freiburg (application no. 493/14 and related amendments) and the local ethics committees of the participating centres. Only patients who provided written consent to participate in the ESID registry can be included in the GAIN registry. They have been informed about the aims and contents as well as about data protection. Participation is voluntary. Consent to participate can be revoked at any time.

Funding
The project was or is funded by the Federal Ministry of Education and Research (BMBF) in the periods of 2019 – 2022 (01GM1910A) and 2023 – 2025 (01GM2206A).

Conflicts of interest
The authors declare that there is no conflict of interest.

Acknowledgement
This study was conducted by the GAIN Registry in collaboration with the ESID Registry and used the ESID online database for data collection. We would like to thank the ESID Registry Working Party for their support and cooperation.

In addition, we would like to thank the participating patients and all those involved in the GAIN Registry.
Research on Rare Diseases in Germany – The GAIN Registry

**References**


10. WHO Collaborating Centre for Drug Statistics Methodology (2022; 2023) ATC classification index with DDDs

11. EMA European Medicine Agency (2020) Article 57 export of ‘Brand name’ for EU authorised medicines
Research on Rare Diseases in Germany – Using small fish and super-resolution microscopy to track down a rare disease

Abstract

**Background:** Focal segmental glomerulosclerosis (FSGS) is a rare disease, or damage to the filtering units of the kidney, the glomeruli, about of which there is only limited knowledge and few treatment options. The STOP-FSGS consortium has set itself the goal to expand our knowledge of this disease and develop new treatment options.

**Project:** Through intensive research and the use of state-of-the-art techniques such as super-resolution microscopy, AI-based imaging and single-cell research, the consortium aims to gain a deeper understanding of the mechanisms of FSGS. This will allow the disease to be diagnosed more accurately and thus enable targeted and more effective treatment of patients. Another focus is on the search for drugs that slow down or even cure the disease.

**Results:** By establishing a rapid animal model, i.e. zebrafish larva, potential substances/drugs were identified that can alleviate FSGS. Moreover, super-resolution microscopy was used to precisely quantify the structural changes in the kidney by determining the so-called ‘filtration slit density’ (FSD) and to identify a marker allowing a personalised prognosis and assessment of the course of the disease.

**Conclusions:** The results obtained help to better recognise the progression of FSGS and to optimally adapt treatment in order to improve the quality of life of the afflicted individuals and avoid renal replacement therapies.

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**FOCAL SEGMENTAL GLOMERULOSCLEROSIS · PERSONALISED DIAGNOSTICS · ZEBRAFISH · SUPERRESOLUTION MICROSCOPY · PODOCYTES · MEDICATION**

**Introduction**

Focal segmental glomerulosclerosis (FSGS) is a rare and complex disease that involves damage to the kidney, in which certain areas of the glomeruli, i.e. of the blood-filtering units of the kidney, are damaged and scarred. In highly industrialised countries such as Europe, it manifests in around 20 individuals per million residents (adults) per year [1]. More than half of adult patients develop chronic or recurrent disease. In around 20% of all children who require lifelong renal replacement therapy, the cause is FSGS [2, 3].

The exact causes and mechanisms of FSGS are not yet understood and may be multifactorial. Due to the lack of specific drugs or other therapeutic options [4], there is an urgent need for further research to deepen the understanding of FSGS and develop new treatment strategies. The acute phase is often treated with immunosuppressants (drugs that inhibit the immune system), particularly high-
Around 80 affected by a rare disease. More than four million people in Germany alone are affected by a rare disease. Around 80% of rare diseases are genetically determined, some diseases cause their first symptoms in childhood. However, the causes of the disease are often unexplored. The relatively small number of people affected, experts and suitable medicines complicate the path to a diagnosis and appropriate therapy. If there is no diagnosis or it can only be made at a late stage, irreversible courses of the disease are often a result. Therefore, research is vital for those affected. Basic research plays an important role here: it not only provides new insights into rare diseases, but can also contribute to a better understanding of more common diseases.

Since 2003, the Federal Ministry of Education and Research (BMBF) has been funding networks that jointly research causes and therapeutic approaches for rare diseases at various university locations. A coordination office supports these networks, among other things, in presenting their results to the public (see also https://www.research4rare.de/wp-content/uploads/2023/05/Poster_R4R_engl_2019-2026.pdf). At the European level, the research consortia are involved in the European Reference Networks (ERN) on rare diseases. In addition, there are international programmes, such as the European Joint Programme on Rare Diseases (EJP RD) for research into the diagnosis and therapy of rare diseases, in which the BMBF also participates.

A disease is considered rare if fewer than five in 10,000 people are affected by such a diagnosis. More than 8,000 rare diseases are known. It is estimated that more than four million people in Germany alone are affected by a rare disease.

Research on Rare Diseases – a funding priority of the Federal Ministry of Education and Research

Research on Rare Diseases in Germany – Focal segmental glomerulosclerosis

FSGS Research is therefore of crucial importance in order to expand our knowledge of the disease and for the development of state-of-the-art procedures for personalised diagnostics and therapy.

**Project**

The STOP-FSGS research network is an association of German FSGS experts. The methods used in the sub-project of the research network presented here were largely developed in the framework of the funding provided by the Federal Ministry of Education and Research (BMBF). These techniques can now be used for diagnostic procedures.

Two methods in particular should be emphasised here: firstly, the method of quantitative analysis of kidney tissue (biopsies) from the kidney using special markers, as well as measurable characteristics of the disease in the blood, are crucial for an early diagnosis and a prognosis of the course of the disease. The more precisely the disease pattern is analysed, the better the subsequent treatment can be.

In order to diagnose functional disorders at an early stage, i.e. before the kidney damage spreads broadly, novel and detailed analyses of the kidney tissue are needed.

However, as in the case of FSGS, this can be very challenging. A truly personalised analysis of tissue samples (biopsies) from the kidney using special markers, as well as measurable characteristics of the disease in the blood, are crucial for an early diagnosis and a prognosis of the course of the disease. The more precisely the disease pattern is analysed, the better the subsequent treatment can be. Advances in diagnostics may help to detect the disease at an early stage and optimise treatment.

In addition, it is important to identify drugs that can slow down or even stop the progression of the disease. This would significantly improve the quality of life of the afflicted individuals and reduce or even eliminate the need for invasive treatments such as dialysis or transplants and the associated risk factors.

Dose glucocorticoids, which have significant short- and long-term side effects. However, there has been little progress made regarding the therapeutic options and the patients’ mortality rate is 50% within five years of the commencement of dialysis, regardless of age.

FSGS leads to an impaired filtration function of the kidney, which is detectable by the formation of oedema and foamy urine. These are important indicators of reduced kidney function, which often leads to kidney failure. In severe cases, only lifelong dialysis or a kidney transplant can ensure the patient’s survival. Dialysis is extremely stressful for the patient and their relatives, though, and often leads to severe cardiovascular disease, which may be fatal.

In order to diagnose functional disorders at an early stage, i.e. before the kidney damage spreads broadly, novel and detailed analyses of the kidney tissue are needed.

However, as in the case of FSGS, this can be very challenging. A truly personalised analysis of tissue samples (biopsies) from the kidney using special markers, as well as measurable characteristics of the disease in the blood, are crucial for an early diagnosis and a prognosis of the course of the disease. The more precisely the disease pattern is analysed, the better the subsequent treatment can be. Advances in diagnostics may help to detect the disease at an early stage and optimise treatment.

In addition, it is important to identify drugs that can slow down or even stop the progression of the disease. This would significantly improve the quality of life of the afflicted individuals and reduce or even eliminate the need for invasive treatments such as dialysis or transplants and the associated risk factors.

**Results and classification**

The STOP-FSGS project consists of several sub-projects, with our research area working on improving diagnostics through the use of super-resolution microscopy and on the identification of curative drugs. The super-resolution...
Focal segmental glomerulosclerosis (FSGS) is a rare and complex disease or damage to the filter units of the kidney for which there are currently only limited treatment options.

By using the super-resolution technique SIM, we can visualize the filtration slit, which is crucial for the proper functioning of the kidney. This method named PEMP can quantify changes in biopsies from patients as well as in animal models. The density of the bright lines is directly linked with the health of this kidney area, meaning the closer the lines are to each other, the healthier this part of the kidney is.

Microscopy technology is a further development of light microscopy and received the Nobel Prize in 2014 [10]. In the STOP-FSGS project, this method was established for use in renal analyses. Using this method, biopsies of patients and experimental kidney samples from animals can now be quantitatively analysed for kidney diagnostics for the first time, and thus precise measurements of kidney changes can be made (Figure 1). This is a significant advance in kidney analysis, as the analysis of structural changes in the fine kidney structures could previously only be done with complex and non-quantitative methods, such as electron microscopy. The use of 3D super-resolution microscopy allows standard biopsies that are routinely carried out in pathology departments and research facilities now to be analysed rapidly, quantitatively and reproducibly. This is now used to calculate a new parameter named filtration slit density (FSD). For the first time, this provides exact values for the kidney changes and, in combination with a marker analysis, even renders a prognosis of the course of the disease possible. Current results demonstrate that this method enables personalised diagnostics for the first time, as precise measurements of the kidney changes associated with FSGS are can be obtained in both patients and laboratory animals [11–13].

In the second research area of the sub-project presented here, a group of substances with the potential to slow down or even stop the development of FSGS was discovered. Using high-throughput screening of zebrafish larvae, which are used as a model organism for FSGS, potential candidates were identified from 138 substances that have a protective effect in FSGS [14]. Due to the great similarity of the simple kidney of zebrafish larvae and human, rat and mouse kidneys, this model is well suited for the investigation of kidney diseases and identification of candidate drugs.

The results of this sub-project promise significant progress in FSGS research and might pave the way for more effective treatments in the future, some of which might also be transferred to other kidney diseases.

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Data protection and ethics
The sub-project of the STOP-FSGS research network presented here is subject to strict compliance with the Animal Welfare Ordinance and the data protection provisions of the EU General Data Protection Regulation (GDPR) and the German Federal Data Protection Act (BDSG). The UMG Ethics Committee has reviewed and approved the ethical aspects (application number BB 166/19).

Data availability
The results/data generated can be used in the framework of a collaboration. Moreover, the data regarding high-content screening are published and can be viewed in the current publication of Schindler et al. 2023 in the ‘Journal of the American Society of Nephrology’ (JASN). In the context of collaborations more details can be requested from the group of authors.

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Conflict of interest
The author declares that the technique of analysis based on super-resolution microscopy has been translated into a start-up called NIPOKA, of which she is CEO.

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Using an established zebrafish model, candidate drugs for the treatment of FSGS have been identified.

The high-resolution super-resolution microscopy allows for more precise diagnostics resulting in a personalised treatment of FSGS.


