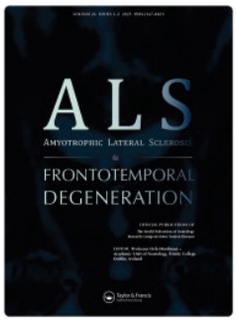

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RESEARCH ARTICLE

SOD1 gene screening in ALS – frequency of mutations, patients' attitudes to genetic information and transition to tofersen treatment in a multi-center program

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Abstract

Objective: To report the frequency of pathogenic *SOD1* gene variants in a screening program in amyotrophic lateral sclerosis (ALS), and the clinical practice of transition to an expanded access program (EAP) of tofersen treatment. *Methods*: From October 2021 to February 2024, at 11 ALS centers in Germany genetic testing for *SOD1*, *FUS*, *TARDBP*, and *C9orf72* was performed. Patients were offered to opt for notification either about all genetic variants or *SOD1* variants relevant for tofersen therapy. The transition to the EAP with tofersen was assessed. *Results*: 1935 patients were screened (94.7% sporadic ALS). 48.8% ($n = 928$) opted for notification of treatment-relevant information. Genetic variants were found as follows: *SOD1* (likely) pathogenic variants (class 4/5) 1.8% ($n = 34$), variants of unknown significance (class 3) 0.8% ($n = 16$), *FUS* (class 4/5) 0.9% ($n = 17$), *TARDBP* (class 4/5) 1.3% ($n = 25$), *C9orf72* hexanucleotide repeat expansion 7.0% ($n = 135$). In *SOD1*-ALS (encompassing class 3–5 variants, $n = 50$), 68.0% ($n = 34$) reported a negative family history. 74.0% ($n = 37$) of *SOD1*-ALS patients – which represent 1.9% of all participants of the screening program –

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were transitioned to tofersen. Median duration from start of genetic testing to treatment was 94 days (57 to 295 days). Eight patients declined treatment whereas five individuals died before initiation of therapy. *Conclusion*: The finding of *SOD1* variants in patients with a negative family history underscores the need for a broad genetic screening in ALS. In *SOD1*-ALS, the treatment option with tofersen was mostly utilized. The wide range in the transition time to tofersen calls for a *SOD1*-ALS management program.

Keywords: *Amyotrophic lateral sclerosis, SOD1 gene, screening, tofersen, transition*

Introduction

Reportedly, 5–10% of people with amyotrophic lateral sclerosis (ALS) have a family history of ALS or frontotemporal dementia (FTD), known as familial ALS (fALS) (1–4). In 1993, a subgroup of ALS patients was linked to mutations in the superoxide dismutase 1 (*SOD1*) gene (5). Subsequently, more than 60 genes were associated with ALS. Among them, *C9orf72*, *SOD1*, *TARDBP* and *FUS* were shown be the most frequent genes being causative for ALS (6,7). Also, in patients who reported a negative family history of ALS pathogenic mutations were found. ALS in which disease-causing mutations can be detected is classified as genetic ALS – regardless of family history. In fact, the reported frequency of genetic ALS in apparently sporadic ALS (sALS) varies considerably – depending on the respective study and on the investigated population (8,9). In a large study of 37 genes in 2340 sALS patients a proportion of 13% with pathogenic genetic variants was shown (10).

The antisense oligonucleotide tofersen was granted accelerated approval by the U.S. Food and Drug Administration (FDA) for the treatment of adult ALS patients who have mutations in the *SOD1* gene (*SOD1*-ALS) (11). In Germany, an expanded access program (EAP) of tofersen was offered from January 2022 to June 2024 (12–14). Only recently, tofersen has been authorized under exceptional circumstances by the European Medicines Agency for the use in the European Union (15). The principal availability of tofersen, either as an approved drug or in an EAP, substantially shifted the relevance of genetic testing. In fact, the detection of a *SOD1* mutation translates into the principal treatment option with tofersen – in patients with and without family history of ALS. Also, for genetic ALS linked to *FUS*, *C9orf72* or *TARDBP*, clinical trials or investigational drug programs are ongoing or under way (16). Thus, the investigation of these genes might also have an individual relevance for the participation in interventional studies or research programs.

Although genetic testing is in principle accessible for people with ALS in Germany, there are in practical terms several barriers for molecular genetic analysis: 1) until recently, genetic testing was basically restricted to fALS. Also, the national diagnostic and treatment guidelines for ALS from August 2021 have not yet endorsed genetic testing of sALS (17). Only with the introduction of tofersen, genetic testing in sALS was gradually introduced in clinical practice but has not yet universally established. 2) The referral process from ALS centers to genetic consultants poses an administrative or logistic barrier to some patients and their families. 3) Appointments with genetic counselors are limited and can translate into waiting lists of up to several months. To lower the entry barriers to genetic investigation, a mutation screening program was introduced as fast-track of genetic testing of 11 specialized ALS centers in Germany. The genetic screening program served as add-on to the standard of care of genetic testing and counseling.

The program encompassed the genetic investigation of *SOD1*, *FUS*, *C9orf72,* and *TARDBP*, and a patient-centered management of genetic information. Genetic information might be perceived as psychologically burdensome and can lead to a subgroup of patients that decide against genetic testing (18–20). Thus, patients were offered two options of genetic information: 1) notification of all results of gene analysis or 2) selected notification of genetic results relevant for tofersen treatment or study participation. As such, patients were reported about (likely) pathogenetic genetic variants in the *SOD1* gene and variants of unknown significance (VUS) as this information was relevant for the transition to tofersen treatment (11–14,21,22). Also, patients with pathogenic *FUS* mutations were informed – provided that the given genetic variant fulfilled the inclusion criteria of an ongoing clinical trial in *FUS*-ALS (NCT04768972).

When analyzing a genetic screening program in clinical practice, this study aimed to 1) investigate the proportion of sALS and fALS, 2) to determine the frequency of pathogenic variants in *SOD1*, *FUS*, *TARDBP* and *C9orf72*, 3) to explore the share of patients that opt-out of full genetic information (and restrict the reporting to therapeutically relevant genetic results), and 4) to assess the transition of *SOD1* mutation carriers to tofersen treatment.

Methods

Study design

This observational study was conducted as a prospective, multicenter, longitudinal cohort study. The investigation was reported according to the STROBE criteria (23).

Participants and definition of cohorts

The participants met the following inclusion criteria: 1) diagnosis of ALS according to the Gold Coast criteria (24); 2) consent to electronic data capture using the research platform "APST" (25); and 3) written consent to genetic investigation.

Setting

Genetic counseling. The genetic screening program was performed in addition and conjunction to the standard of care of genetic testing and counseling in Germany which is described in the Supplement Methods S1.

Genetic testing. The screening of *SOD1*, *FUS*, *TARDBP* and *C9orf72* was subject of the study and covered by a research grant (Supplement Methods S1).

Recruitment. Following informed consent, patients were recruited at 11 multidisciplinary ALS centers in Germany between October 2021 and February 2024.

Informed consent and notification about genetic study results. Informed consent was organized in a multi-step process of 1) patient information, 2) genetic counseling prior to study participation, 3) written informed consent and selection of modalities for the notification of genetic study results. Study participants were requested to select one of the two options of notification about individual study results—option 1: notification about all genetic study results, option 2: notification about selected genetic study results with relevance for potential treatment or study participation. Thus, notification encompassed all (likely) pathogenic variants and VUS of the *SOD1* gene. Furthermore, patients with (likely) pathogenic *FUS* mutations were informed. Notification about *FUS* variants was restricted to the inclusion criteria of an ongoing clinical trial in *FUS*-ALS (NCT04768972).

Data collection. Demographic and clinical data were obtained from electronic health records. Classification of the ALS phenotype and rating of the ALS function rating scale – revised (ALSFRS-R) was performed by qualified evaluators (26).

Blood sample collection. The collection of human peripheral venous blood was performed according to the respective standard operating procedures of each center.

Transition to tofersen therapy. The transition to tofersen treatment is a multi-step process of genetic screening, followed by consulting, decision-making, and eventually intrathecal application of the drug. Treatment with tofersen was not available in all participating ALS centers. Therefore, a case management to treatment-performing ALS centers was established (Supplement Methods S1).

Molecular genetic analysis and bioinformatics analysis

Molecular genetic analysis was performed by a certified genetic laboratory (ARCHIMED Life Science GmbH, Vienna, Austria) using a validated and accredited method. Genomic DNA was isolated from EDTA blood, using Chemagic 360 extraction instrument and DNA isolation kit (PerkinElmer, Waltham, MA, USA). DNA libraries for the enrichment of the genes *SOD1*, *TARDBP* and *FUS* were prepared using the AmpliSeq Sequencing technology (Illumina, San Diego, CA, USA). The entire coding region and flanking intronic regions was covered in all cases with at least factor 30. Sequencing was performed on an Illumina HiSeq 2500 platform (Illumina). Variant calling was performed using the DRAGEN pipeline (Illumina). Alignment of sequence reads to the human genome (GRCh37) was performed. MANE Select reference sequences were used (*SOD1*: NM_000454.5, *TARDBP*: NM_007375.4, *FUS*: NM_004960.4). The genetic nomenclature refers to the Human Genome Variation Society (HGVS). Variants were classified based on the guidelines of the American College of Medical Genetics and Genomics (ACMG) as follows: benign (class 1), likely benign (class 2), variant of uncertain significance (class 3, VUS), likely pathogenic (class 4), and pathogenic (class 5) (22,23). Class 3, 4 and 5 variants were reported. High-resolution genotyping of hexanucleotide repeat expansions (HRE) in the *C9orf72* gene was carried out by AmplideX® PCR/CE *C9orf72* Kit (Assuragen, Austin, TX, USA) in all cases. Southern blot analysis was performed additional when indicated. Repeat sizes $<20\,G_4C_2$ repeats were not reported.

Protocol approvals and registrations

The study protocol was ethically approved under the number EA1/128/21. A signed informed consent form was obtained from all study participants.

Variables

Demographic and clinical characteristics. The following demographic and clinical characteristics were collected: age at disease onset, sex, disease duration (number of months between disease onset and study inclusion), and ALSFRS-R (26).

Frequency of familial and sporadic ALS. The number and degree of relatedness of family members who are living with ALS (or FTD) or who died of ALS (FTD) were assessed. Details of the assessment of family history are provided in Supplement Methods S1.

Frequency of genetic variants. Genetic variants of the *SOD1*, *FUS* and *TARDBP* genes and pathogenic HRE of *C9orf72* were assessed. Detailed information about the genetic variant (substitution,

deletion, insertion, duplication inversion) and location were collected. Pathogenicity of genetic variants was classified according to the ACMG guidelines (27).

Patients' preferences for notification on genetic information. Study participants were requested to select one of the two options of notification about individual study results. The proportion of patients that opted for option 1 (notification about all genetic results) versus option 2 (notification about genetic variants with relevance for potential treatment or study participation).

Transition of SOD1-ALS patients to tofersen treatment. The transition of SOD1-ALS patients to tofersen treatment was assessed. The following data were obtained: number of patients that i) declined tofersen therapy, ii) deceased before start of treatment, or iii) were included in tofersen EAP. The latency from the day of blood sampling to delivery of genetic laboratory results to the ALS center was defined as turnaround time (in days). The duration from the genetic testing to treatment was determined by means of needle-to-needle time referring to the latency from blood sampling (needle 1) to the intrathecal injection of tofersen (needle 2).

Statistical methods

Statistical analyses were performed using SPSS (IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY, USA). Descriptive statistics were used (frequency in percent, mean, median, and ranges) and data analyzed using Statplus (Version7.7.11). Continuous variables were assessed for normality using the Shapiro-Wilk test and described accordingly as mean, standard deviation (SD) or median and interquartile range (25th–75th percentile). For comparison of the frequency of fALS between the four groups of genetic ALS, a χ^2 test was performed.

Results

Demographic and clinical characteristics

The demographic and clinical characteristics of the total cohort and in patients with class 4/5 variants of the *SOD1*, *FUS* and *TARDBP* genes and pathogenic HRE of *C9orf72* are shown in Table 1.

Frequency of familial and sporadic ALS

94.7% ($n = 1833$) and 5.3% ($n = 102$) of total cohort were classified as sALS or fALS, respectively. Also, most patients with genetic variants in the genes of *SOD1* (68.0%, $n = 34$), *FUS* (81.0%, $n = 17$) and *TARDBP* (79.3%, $n = 23$) or pathogenic HRE of *C9orf72* (85.0%, $n = 130$) had a negative family history of ALS (sALS). The proportion of fALS in *SOD1*-ALS (32.0%) was higher compared to *FUS*-ALS (19.0%) and *TARDBP*-ALS (20.7%), however these differences were not significant ($p = 0.410$; $p = 0.412$). In *C9orf72*-ALS, the frequency of fALS was even lower (15.0%) and reached statistical significance ($p = 0.014$). The proportion of sALS and fALS in the total cohort and in the four groups of genetic ALS are shown in Table 1 and Figure 1 and Figure 2.

Frequency of genetic variants

Among the four investigated genes, the most common pathogenic genetic variant was found in *C9orf72* HRE (7.0%, $n = 135$), followed by class 4/5 variants in *SOD1* (1.8%, $n = 34$), *FUS* (0.9%, $n = 17$), and *TARDBP* (1.3%, $n = 25$). Furthermore,

Table 1. Results of genetic screening.

Patients (%)	Total 1935	*SOD1* 50 (2.6%)	*FUS* 21 (1.1%)	*TARDBP* 29 (1.5%)	*C9orf72* 153 (7.9%)
Age (years)	63 (21–94)	56 (32–78)	60 (25–77)	65 (38–85)	60 (32–83)
Male/ female	1141 (59.0%) 749 (41.0%)	26 (52.0%) 23 (48.0%)	12 (57.0%) 9 (43.0%)	17 (59.0%) 12 (41.0%)	71 (46.0%) 82 (54.0%)
Duration (months)	39 (0–550)	55 (0–235)	29 (5–109)	37 (8–100)	21 (0–187)
ALSFRS-R (min-max)	33 (0–48)	33 (14–47)	35 (11–46)	32 (11–46)	35 (0–48)
Sporadic ALS	1833 (94.7%)	34 (1.8%)	17 (0.9%)	23 (1.2%)	130 (6.7%)
Familial ALS	102 (5.3%)	16 (0.8%)	4 (0.2%)	6 (0.3%)	23 (1.2%)
Class 4/5	76 (3.9%)	34 (1.8%)	17 (0.9%)	25 (1.3%)	–
Class 3	21 (1.1%)	16 (0.8%)	2 (0.1%)	3 (0.2%)	–
HRE	135 (7.0%)	–	–	–	135 (7.0%)
Class 4/5 or HRE	211 (10.9%)	–	–	–	–

Abbreviations: ALS, amyotrophic lateral sclerosis; ALSFRS-R, ALS functional rating scale revised. Class 5, pathogenic variant; class 4, likely pathogenic variant; class 3, variant of uncertain significance according to the guidelines of the American College of Medical Genetics and Genomics (ACMG); Duration, ALS duration in months; HRE, hexanucleotide repeat expansion.

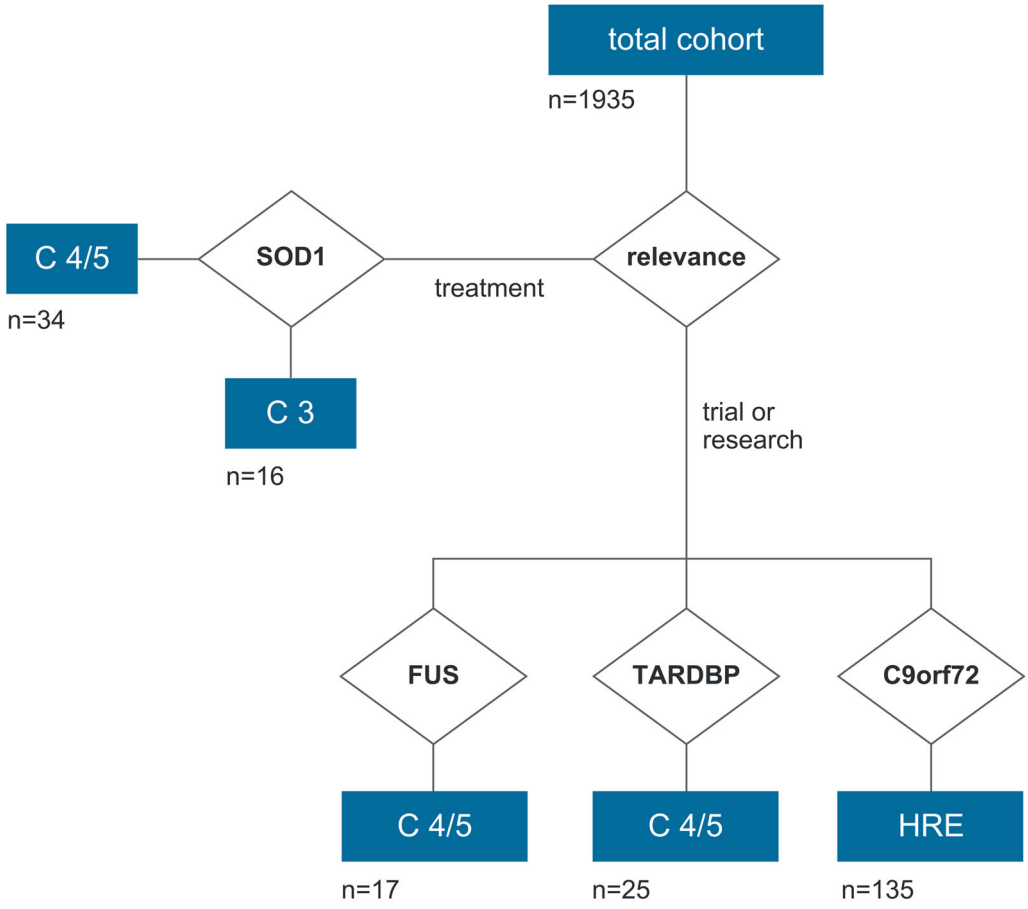

Figure 1. Results of genetic screening. n = number of ALS patients with genetic variants. C5, pathogenic (class 5) variant; C4, likely pathogenic (class 4) variant; C3, variant of uncertain significance (class 3) according to the guidelines of the American College of Medical Genetics and Genomics (ACMG); HRE: hexanucleotide repeat expansion.

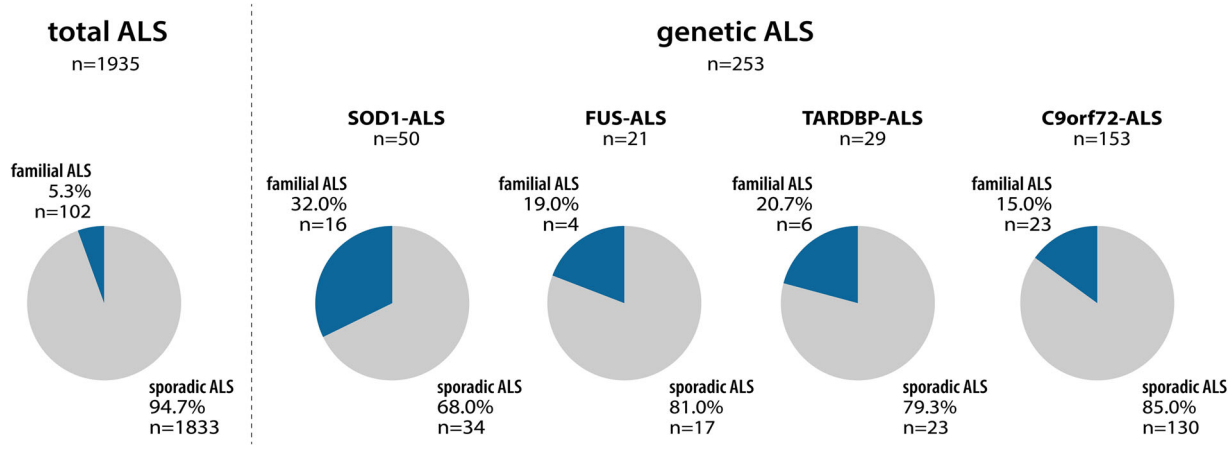

Figure 2. Proportion of sporadic and familial ALS. Sporadic ALS, no family history of ALS; familial ALS, family history of ALS; genetic ALS, ALS patients with pathogenic (class 5) or likely pathogenic (class 4) variants according to the guidelines of the American College of Medical Genetics and Genomics (ACMG) in *SOD1, FUS* and *TARDPB* or hexanucleotide repeat expansion in *C9orf72*.

in 0.8% ($n = 16$) class 3 variants of in the *SOD1* gene were found (Table 1, Figure 1). Detailed information about genetic variants is given in the supplement (Table S1).

Patients' preferences for notification on genetic information

49.4% ($n = 906$) of study participants opted for the notification about all genetic results (option 1), whereas 50.6% ($n = 928$) of patients preferred the selected notification about genetic variants with relevance for potential treatment or study participation (option 2) (Table 2). Among female participants, a slight predominance for option 1 was found (53.3%) whereas male patients to the same extent preferred the option 2 (53.3%). A strong difference in the patient's preferences was found between sALS and fALS patients. Most patients

Table 2. Patient's preferences for notification of screening results.

Preferences	Option 1 all information	Option 2 selected information	Undecided	Total
Genes	*SOD1, FUS, TARDBP, C9orf72*	*SOD1*	–	–
Notification	No variant, class 1–5, HRE	Class 4/5 (3)	–	–
Male	505 (55.7%)	577 (62.2%)	40 (59.7%)	1122 (59.0%)
Female	401 (44.3%)	351 (37.8%)	27 (40.3%)	779 (41.0%)
Sporadic ALS	845 (93.3%)	896 (96.6%)	60 (89.6%)	1801 (94.7%)
Familial ALS	61 (6.7%)	32 (3.4%)	7 (10.4%)	100 (5.3%)
Total cohort	**906 (47.7%)**	**928 (48.8%)**	**67 (3.5%)**	**1901 (100%)**

Class 5, pathogenic variant, class 4, likely pathogenic genetic variant; class 3, variant of uncertain significance; class 2, likely benign genetic variant; class 1, benign genetic variant according to the guidelines of the American College of Medical Genetics and Genomics (ACMG); HRE, hexanucleotide repeat expansion.

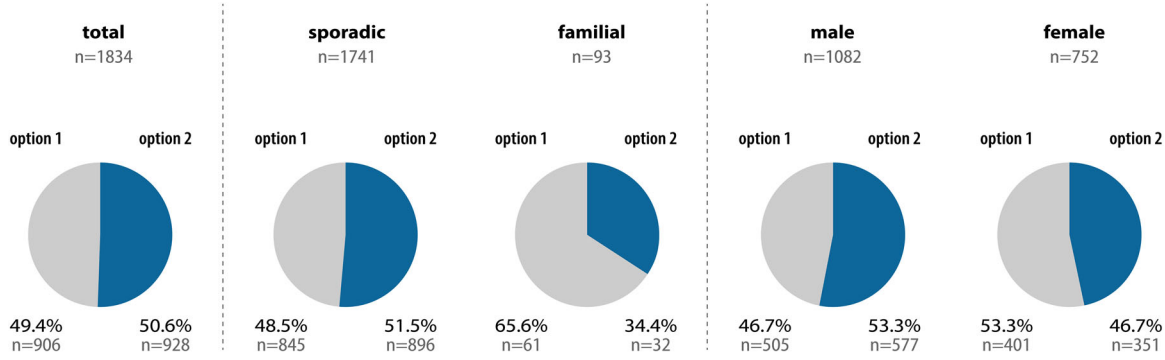

Figure 3. Patients' preferences for genetic information. Patients were offered two options of genetic information: option 1: notification about all genetic variants; option 2: information about *SOD1* variants being relevant for tofersen therapy. Sporadic, sporadic ALS; familial, familial ALS.

with fALS preferred to be informed about all genetic results (65.6%) (Table 2, Figure 3).

Transition of SOD1-ALS patients to tofersen treatment

74.0% ($n = 37$) of *SOD1*-ALS patients opted for the EAP with tofersen. 16.0% ($n = 8$) individuals opted against tofersen therapy whereas 10.0% ($n = 5$) deceased before start of treatment (Table 3).

The median turnaround time from blood sampling to delivery of genetic laboratory results was 51 days (minimum 19 days, maximum 100 days). Median latency (needle-to-needle time) from blood sampling (needle 1) to start of tofersen treatment (needle 2) was 121 days (minimum 57 days, maximum 295 days) (Figure 4).

Discussion

In this study, a mutation screening program alongside clinical practice was performed. Fifty patients with genetic variants in the *SOD1* gene were identified of whom 37 have been transitioned to an EAP of tofersen treatment. In addition, and with less therapeutic relevance, the genes of *FUS*, *TARDBP* and *C9orf72* were investigated.

Table 3. Transition of SOD1-ALS patients to tofersen treatment.

	Number (n = patients)	Time (days)* Median (IQR)	Min-Max
Testing			
Result reported	50	46 (42–64)	19–100
Decision making			
Declined	8	–	
Deceased	5	–	
Consented	37	–	
Treatment			
Treated	37 (74.0%)	94 (68–143)	57–295

*Analysis of subgroup with de novo identification of therapeutically relevant variant in SOD1 ($n = 30$).
Min: minimum; Max: maximum; IQR: interquartile range.

The frequency (1.8%) of *SOD1* class 4/5 variants was in the order of prior reports in Germany, and higher compared to other studied populations (3,4,8–10). Another 0.8% of participants ($n = 16$) showed *SOD1* class 3 variants including seven patients with the heterozygous p.D91A ($SOD1^{D91A}$, c.272A > C) variant (Figure 1). Given the unique position of p.D91A distinct from other *SOD1* mutations, and its potential pathogenicity, these $SOD1^{D91het}$ patients were treated with tofersen (20,27–31). Therefore, $SOD1^{D91het}$ mutations and other class 3 *SOD1* genetic variants can be assigned to the group of therapeutically relevant mutations

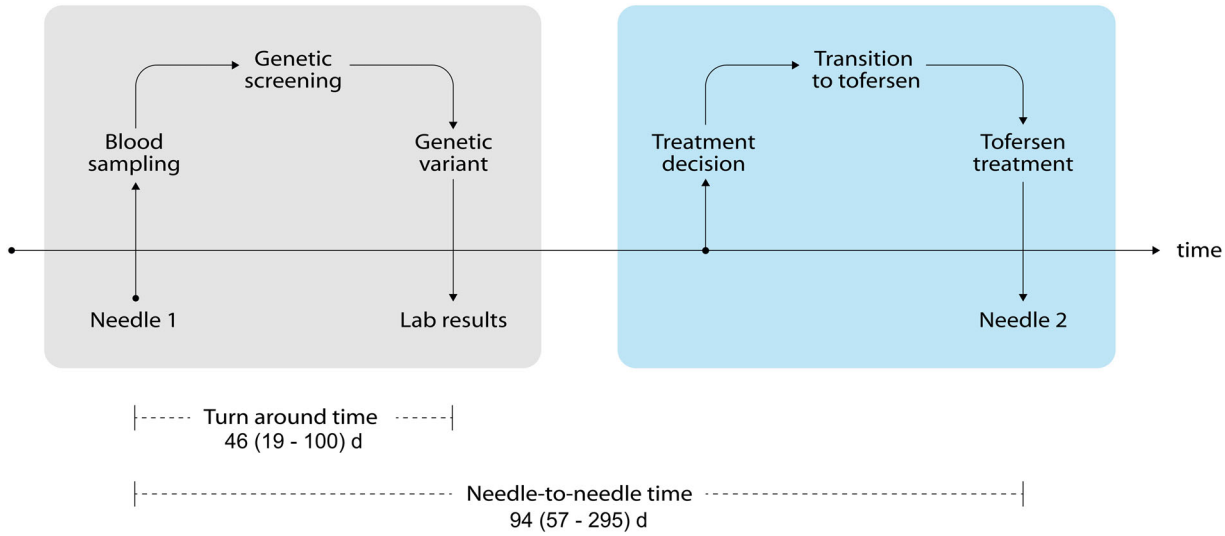

Figure 4. Transition to tofersen treatment. The pathway to tofersen treatment is a multi-step process of genetic screening, followed by the transition of *SOD1* mutation carriers to the intrathecal application of tofersen. Turnaround time, latency from the day of blood sampling to delivery of genetic laboratory results to the ALS center); needle-to-needle time, latency from blood sampling (needle 1) to the intrathecal injection of tofersen (needle 2); d, days.

(21). The proportion of patients with HRE in the *C9orf72* gene (7.9%) was in line with previous reports. However, class 4/5 variants of the *FUS* and *TARDBP* genes were more frequent than previously reported (8–10).

Systematic assessment of family history of ALS and FTD revealed fALS in 5.3% of the studied cohort. This proportion of fALS corresponds to an epidemiologic metanalysis that showed fALS in 5.2% of ALS patients (9). However, as the classification of fALS is based on reported family history methodological variation in the assessment could underestimate the prevalence of fALS. Conversely, reports of higher frequency of fALS might be explained by population genetic differences in the studied cohorts or an observation bias of genetic registry studies (7). Although fALS was found in about one third of patients, more *SOD1* mutation carriers can be expected among ALS patients without family history of ALS. This observation was in conjunction with previous studies and underscored the need to provide access to genetic screening in ALS patients, including those individuals with apparently sporadic ALS (9).

Few studies focused on the patient's attitudes toward genetic testing, and the willingness to learn about genetic variants in ALS-causing genes (18–20). In this investigation, the screening was preceded by an individual decision-making on the notification of genetic laboratory results. Only half of study participants (47.7%) opted for the notification about all genetic results (option 1), whereas remarkable proportion of the other half preferred the notification about therapeutically relevant variants only (option 2). In this decision-making, a gender difference was found in which male patients more often preferred option 2 whereas female participants showed a tendency toward option 1. The reasons for the differences are not understood and need further investigation before any conclusion can be drawn from this observation. The decision-making in fALS was remarkable from two angles. The finding that most fALS patients opted for full information (65.6% option 1) demonstrated that a positive history of ALS led to a higher request of full genetic information compared to sALS. Conversely, the 34.4% of fALS patients opting for restricted genetic information (option 2) underlined the need of a subgroup of fALS patients to be protected from unintended genetic information. This result can be interpreted that these fALS patients perceived genetic information as burdensome which is the main motivation for option 2. The specific reasons for the decisions were beyond the scope of this investigation and therefore not captured. Although the genetic consulting and decision-making process itself have not been assessed, it is conceivable that differences of the patients' decisions might reflect variabilities of attitudes, qualification, and consultation standards among individual physicians and ALS centers. This finding contributes to the notion that genetic consultation standards need to be developed, implemented, and continuously adapted to the evolving knowledge (32,33).

The genetic screening program was performed in the context of the emerging treatment option with tofersen in patients with *SOD1*-ALS (11–15,21,22). Therefore, this study granted first insights in the transition to tofersen in clinical practice. At the end of the observation period of the study, 74.0% of *SOD1*-ALS patients were transitioned to tofersen therapy representing 1.9% of the screened ALS cohort. Five patients (10.0%) died before the start of treatment. With a broader implementation of this therapy, it can be expected

and must be achieved that patients get fast access to tofersen. Also, genetic diagnostics early after diagnosis should also contribute to prevent patients from receiving treatment only in progressed stages of the disease. A smaller proportion of *SOD1*-ALS patients (26.0%) have not received treatment – either because the patients had died ($n = 5$) before the start of treatment or because therapy was refused ($n = 8$). The reasons for refusal were not systematically recorded. The limited information available did not show an obvious correlation with age, disease duration or functional deficit (Table S2). However, it is noteworthy that all participants who refused treatment were female patients. Two other patients in whom a *SOD1* mutation was identified have indicated a complex constellation. These patients have dedicated their genetic results exclusively to research and refrained from the notification of any genetic information, even if it has therapeutic relevance - a case that has now occurred. The reasons for the patient's decision to decline genetic information or therapy needs to be addressed in future research. The gender imbalance observed to date deserves special attention. This research has to ensure that the withholding of genetic information and/or treatment is the result of an informed and shared decision-making process and not the expression of barriers to access (e.g. availability of information, specialist advice, transportation). This number of patients is also likely to change in the future as treatment is included in guidelines, awareness increases, and more treatment experiences are published from a neurological and direct patient perspective. Digital channels, in particular patient forums and exchange platforms, will make an important contribution to the dissemination of patient experience (34).

In addition to *SOD1*, three other ALS genes were investigated that are not only common but have also been identified as therapeutic targets in clinical trials or individual treatment programs. Thus, four patients detected in the screening program were recommended and transferred to the clinical trial with ION363, an antisense oligonucleotide and investigational drug for individuals with *FUS* mutations (NCT04768972). The screening for *C9orf72* HRE was also motivated with the perspective of potential therapeutic relevance. However, two clinical trials with antisense oligonucleotide on *C9orf72* (NCT04931862, NCT04288856) were terminated prematurely, so that there was no immediate relevance for participation in an EAP and a clinical study during the observation period of this study (35). For patients with genetic variants in *TARDBP*, there was also no prospect of participation in an EAP, a clinical trial, or another experimental therapy.

The transition from the genetic result to the actual treatment is not self-fulfilling but an active patient management process. It includes consulting about the benefits and risks of treatment, decision-making and case management to coordinate the patient to one of the specialized centers offering intrathecal application of tofersen. For the time lag between genetic diagnostics of *SOD1* (as part of a screening program) to the initiation of treatment, the term of needle-to-needle time has been used. This time was coined in deliberate analogy to the door-to-needle time in stroke treatment pathways and the related time-is-brain concept (36–38) Given the time-is-function reality in ALS, a fast treatment must be viewed as an imperative in tofersen therapy (39,40). The median latency (needle-to-needle time) for the tofersen treatment was rather high (94 days, 3 months) and demonstrated a remarkable range (minimum 57 days; maximum 295 days). This observation comes with some limitations. The genetic screening study began at the end of 2021, while the EAP was not implemented in practice until March 2022. Therefore, only patients from 2022 onwards, and thus a smaller cohort, were evaluated in terms of transition. Also, the reasons for treatment delay and variability in transition process were not systematically assessed and analyzed. Notwithstanding this limitation, the results suggested that the availability of the therapy alone is not a self-fulfilling condition for immediate treatment. To ensure broad and timely access to therapy, a tofersen patient management program seems mandatory.

In conclusion, screening for genetic variants in *SOD1* as part of the diagnostic workup in ALS was found effective for detecting *SOD1* mutations and can enable timely therapy with tofersen. The findings of latencies to treatment and, that a subgroup of *SOD1*-ALS patients have not yet received access, emphasizes the need for the definition and harmonization of diagnostic standards and treatment pathways with tofersen as prototype and pioneer for the just beginning era of genetic therapy in ALS.

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Author's contribution

TM, PS, AM and PK designed and conceptualized the study, analyzed, and interpreted the data, and drafted the manuscript for intellectual content. TG, UW, SP, AR, RS, JG, SB, PW, JW, RG, MV, PB, MM, JW, BS, DCK, YC, DK, JN, PS, BW and CM had a major role in data acquisition and revised the manuscript for intellectual content.

Declaration of interest

TM has received grants, personal fees, non-financial support and research support from AL-S Pharma, Amylyx, Cytokinetics, Ferrer, Mitsubishi Tanabe, Sanofi, Orphazyme, and served on the advisory boards of Amylyx, Biogen, and ITF Pharma outside of the submitted work. TM and CM are founders and shareholders of the Ambulanzpartner Soziotechnologie APST GmbH, which makes the mobile application "ALS-App." TG has received personal fees from ITF Pharma and served on the advisory boards of Amylyx and ITF Pharma outside of the submitted work. SP has received speaker fees, non-financial support and research support from Biogen, Roche, ALS Pharma, Amylyx, Cytokinetics, Ferrer, ITF Pharma, and Sanofi and served on advisory boards of Amylyx, Biogen, Roche, Zambon and ITF Pharma outside of the submitted work. PW has served on advisory boards of Biogen, ITF Pharma and Novartis outside of the submitted work. RG has received grants, personal fees, non-financial support and research support from Biogen and served on the advisory boards of Biogen, Roche, and ITF Pharma outside of the submitted work. MV received travel expenses and non-financial support from ITF Pharma outside of the submitted work. AM has received personal fees, non-financial support, and research support from ITF Pharma and Zambon outside the submitted work. PK received consulting fees from Biogen. The other authors declare no conflicts of interest.

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Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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