

The Desire for Pre Symptomatic Treatment in the At Risk Genetic ALS and FTD Community

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Introduction

We are a group of people at risk of genetic ALS/FTD organized as the Familial ALS Team. The number of people who know they are at risk for developing genetic ALS/FTD grows every year with the increased uptake in genetic testing in ALS and FTD.

The prospect of gene therapies targeted against pathogenic variants of SOD1, C9orf72, and FUS has raised clinical research interest in people at risk of genetic ALS, and at least one trial (BIIB067/ATLAS¹) aims to initiate an experimental treatment pre-symptomatically in ALS/FTD. In a clinically adjacent area, carriers of FTD-associated GRN mutations are being recruited into a pivotal phase 3 trial targeting the GRN mutation (AL001/INFRONT-3²). Given this, we sought to understand how our community felt about access to pre-diagnosis therapies and to explore the risks and inconveniences we would tolerate for different efficacy profiles.

Methods

- Online anonymous survey on Google Forms.
- As a volunteer team surveying our community independently we did not seek ethics approval
- Inclusion criteria: participants over the age of 18 and at risk for genetic ALS and/or FTD.
- Exclusion criteria: people already diagnosed with ALS/FTD, as well as those in genetic ALS/FTD families who tested negative for their family's mutation.
- The survey was advertised via email and social media including Twitter, Reddit, private Facebook groups for Familial ALS and C9orf72, and message forums for ALS and dementia.
- Launched Friday September 30th, 2022 and was closed to new responses on Friday October 21st, 2022.

Results

- 197 total survey responses; 174 after exclusion criteria
- Respondents ranged in age from 18-86+, with most between the ages of 36-55.
- 72.9% of respondents identified as female and 95.3% reported their race as White/Caucasian.
- 72% from the US, followed by the UK (10%), Canada (9.4%), Europe (3.5%), Australia (2.9%), and the rest of the world (1.7%).

Most respondents (120/174, 69%) reported that they would be interested in treatment as early as possible, even absent any clinical symptoms or biological signs of disease activity (Figure 1). A minority (43/174, 24.7%) would only be interested at the first biological signs of disease activity i.e. for a biomarker signal, and just a fraction (9/174, 5%) were interested only when symptoms first appear. **Only 4 out of all eligible respondents (174) reported not being interested in presymptomatic treatment.** The survey then ended for those respondents.

If a regulatory agency such as the FDA approved a treatment for ALS/FTD in trials only conducted with symptomatic patients then 165/170 (97%) of eligible respondents said they would consider taking it pre-symptomatically (Figure 2), with a majority (99/170, 58%) limiting their interest to approved treatments that were genetically targeted or if the treatment's impact on the patient could be measured.

We inquired what threshold of side effects respondents would be willing to allow for access to treatments of varying levels of efficacy, judged in this situation by how long a hypothetical treatment would delay symptoms that would interfere with daily living. **The responses showed a willingness to accept greater side effect burden for more effective treatments. (Figure 3)** For a treatment with the ability to only delay major symptoms by 1 year, 63.5% (108/170) would accept less severe side effects. **Tolerance for more severe symptoms grew from 8.2% (14/170) in the 1 year delay scenario to 49.4% (84/170) for a permanent delay. 28.2% of respondents (48/170) would not accept any side effects or answered they were unsure or did not want to share for the 1 year delay, while only 10% (17/170) felt that way for the permanent delay.**

Discussion

Our survey results indicate that those who are at risk for genetic ALS/FTD have a strong desire for pre-symptomatic treatment.

While this may be considered intuitive, our survey is the first attempt to arrive at an analysis as to how widespread that feeling is in those at risk.

As new therapies become available, it is important for those designing trials, regulating drug labels, and potential prescribing physicians to accept the need and willingness of this population to accept side effects and inconveniences of medical therapy for different levels of efficacy.

We may need to conduct further investigations to ascertain if there are added benefits, if any, for earlier use of the currently approved disease modifying drugs in ALS in those at risk.

This is evidenced as most respondents were only interested in ALS treatments approved based on symptomatic patient trials if those treatments had characteristics absent in the 3 approved drugs (genetically targeted or with the ability for a patient to measure the effect of the treatment on them.)

Limitations

- Small sample size; may not represent the opinions of all pre-symptomatic ALS/FTD gene carriers.
- Many at risk individuals do not yet know they are at risk due to lack of universal genetic testing in ALS and FTD.
- People who find the topic of their future risk distressing or of no consequence may have chosen not to participate, so our sample is biased to those most engaged and educated about ALS/FTD.

174 responses

Figure 1: Desire for Pre-symptomatic Treatment

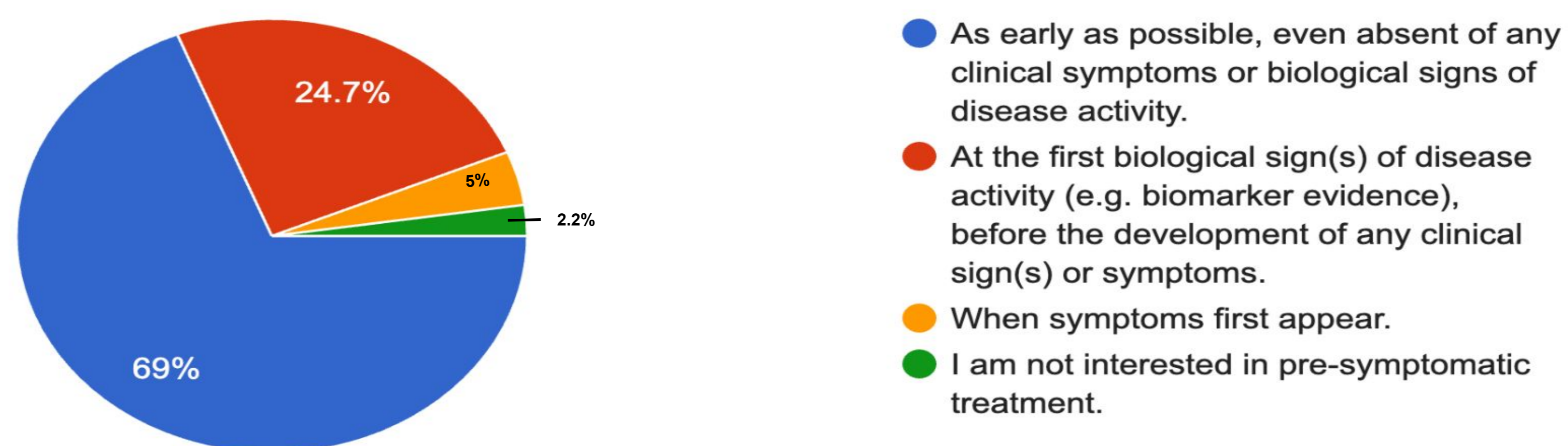


Figure 2: Interest in Treatments only trialed with symptomatic patients (multiple choices accepted)

170 responses

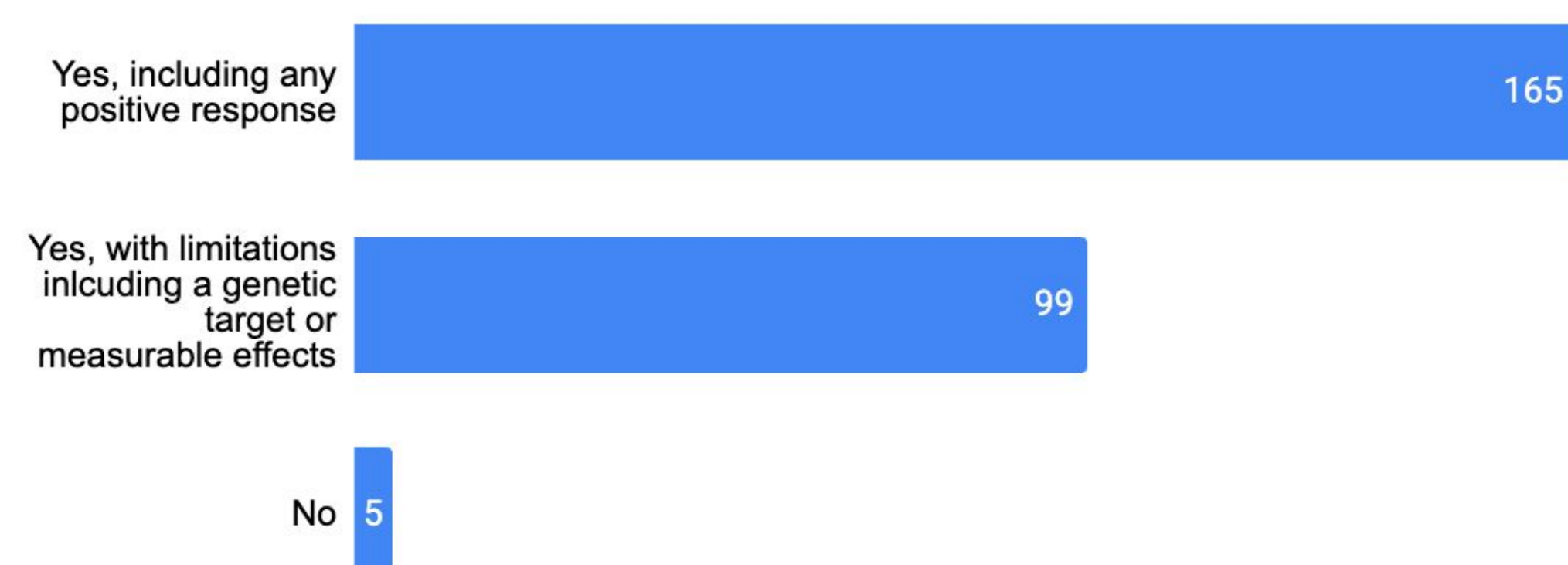
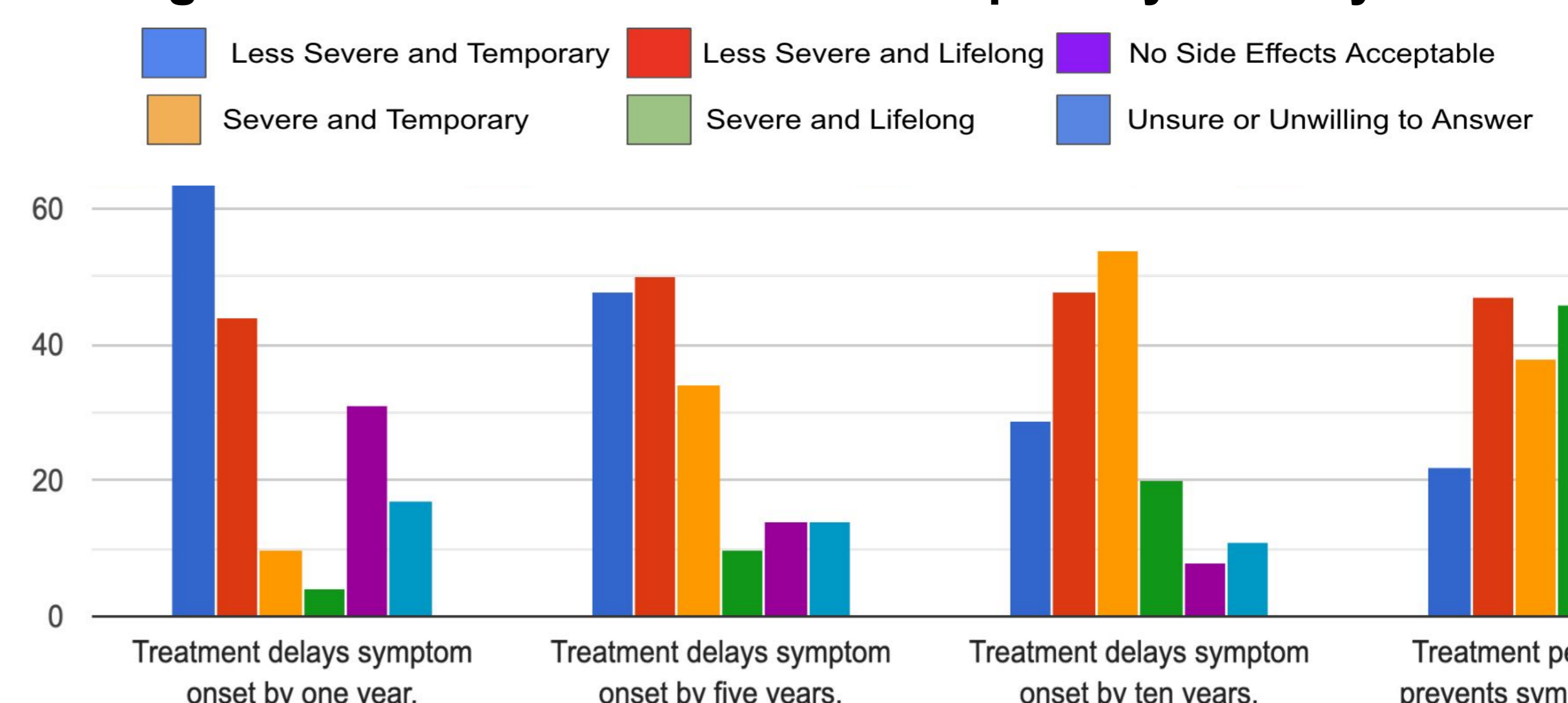


Figure 3: Level of Side Effects accepted by efficacy of treatment



Data Availability

These data are available upon request for ALS/FTD researchers interested in analyzing the responses in more detail. Email jean.swidler@gmail.com.

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References

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