Estimating the Size of the Asymptomatic Genetic ALS & FTD Community in the United States

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Introduction

We are Genetic ALS & FTD: End the Legacy, a patient-led group representing the interests of and providing resources to the genetic ALS & FTD community.

We offer an estimation of the population of genetic ALS and FTD asymptomatic carriers with the understanding that:

- The genetic community is often only considered as a minority of people with an active ALS or FTD diagnosis
- Extensive families with multiple affected generations and branches exist that are at risk for these genetic diseases
- Multiple gene-targeted therapies are approved or in trial
- Intervening before symptoms start is the prudent path forward
- The estimations are not an actual count of people due to reliance on imperfect assumptions of incidence and genetic data
- This is a valuable tool to assess the scope of these conditions and the needs of those impacted
- Presymptomatic refers to those genetic carriers who will develop disease
- Asymptomatic refers to both those genetic carriers who will develop disease and those who will not due to incomplete penetrance.

Method

- Currently accepted assumptions (Table 1) about ALS and FTD can provide a reasonable estimation of the entire population of gene carriers who would develop the disease at some point in life.
- This can be done by taking the share of ALS and FTD incidence linked to genetics and inheritance and multiplying it by the average age of disease diagnosis for that gene. For example, SOD1 ALS is implicated in between 1.88% and 2.56% of all ALS[4], resulting in an estimated range of 106.8 and 205.34 incident SOD1 ALS cases a year in the United States. The observed average age of diagnosis for SOD1 ALS is 49.76. Multiplying the incidence by the average of onset provides a presymptomatic SOD1 population estimate of between 5,308 and 10,205 in the United States.
- We used low and high assumptions to provide a range for the estimations. The low and high comprise the lower and higher bounds of genetic share of disease and overall disease incidence. We provide a table of the assumptions used in Table 1 and the estimation of the presymptomatic genetic ALS & FTD population in Figures 1, 2 and 3 below.
- The above does not account for how many asymptomatic carriers are in total, as it does not account for incomplete penetrance.
- To arrive at the estimate of the population of gene carriers who are alive but who will not develop ALS or FTD, we can take the proportion of incomplete penetrance for that gene for each incident year cohort and multiply it by the average length of life for all people. Adding the population of carriers who will not develop disease to the population of presymptomatic carriers, we can arrive at the full asymptomatic carrier population estimate. The low and high assumptions are maintained, and possible penetrance of 90% and 70% are shown in Figures 4 and 5.

Limitations

- We have provided a range to account for our calculations based on estimates which may be inherently flawed
- As we are estimating off of estimates there is a chance to be far from the truth. In providing a range we have attempted to limit this.
- Our method does not account for individuals who may have received a dual ALS & FTD diagnosis and as such some portion of the ALS & FTD share of disease may be double counted.

Assumption	Low	High
Incident ALS (Per 100K)	1.71	2.42
Incident FTD (Per 100k)	2.73	4.13
Share of ALS that is Familial	5% [4]	10% [4]
Sporadic ALS relative to Familial ALS	95%	90%
Genetic / Inherited Share of all FTD		
MAPT	5% [5]	10% [5]
GRN	5% [5]	10% [5]
C9orf72	5% [5]	10% [5]
Other Inherited FTD	5% [5]	10%
Genetic / Inherited Share of all ALS		
Sporadic C9orf72 Share	4.85%[4]	4.59%[4]
Familial C9orf72	1.67%[4]	3.37%[4]
SOD1	1.88%[4]	2.56%[4]
TARDBP	0.97%[4]	1.14%[4]
FUS	0.43%[4]	0.55%[4]
All Other Inherited ALS	2.23%[4]	4.45%[4]

Figure 1

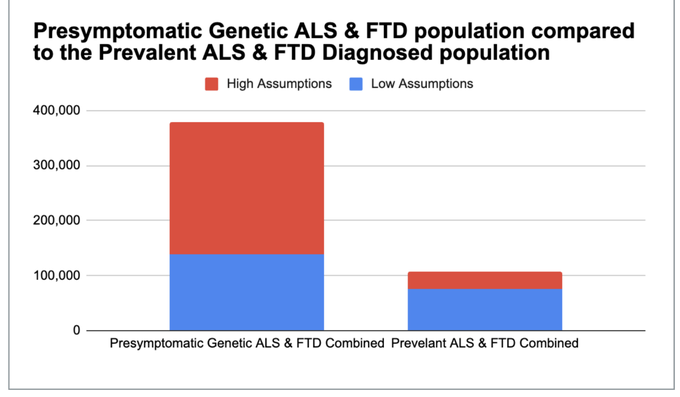


Figure 2

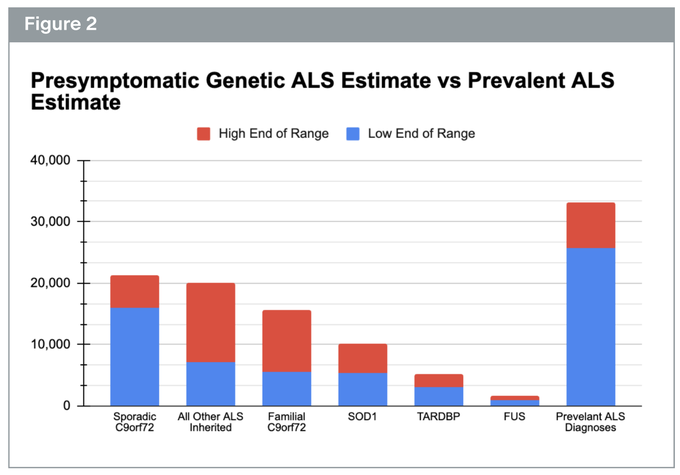


Figure 3

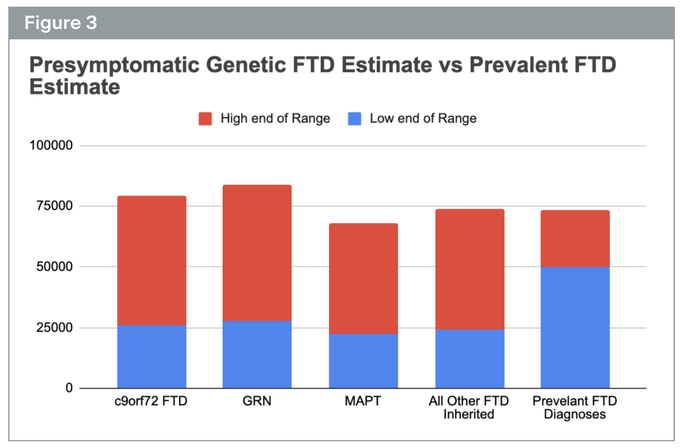


Figure 4

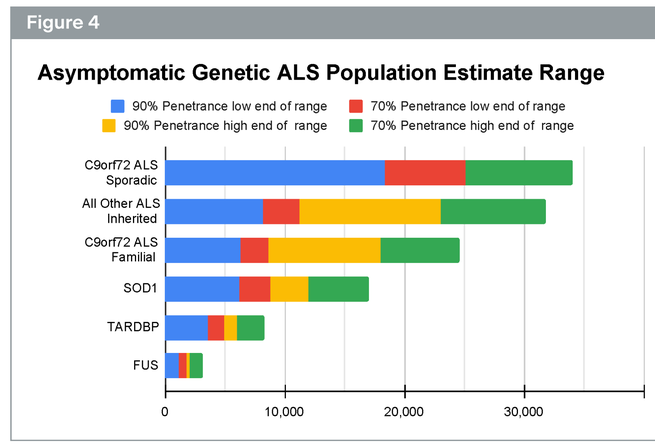
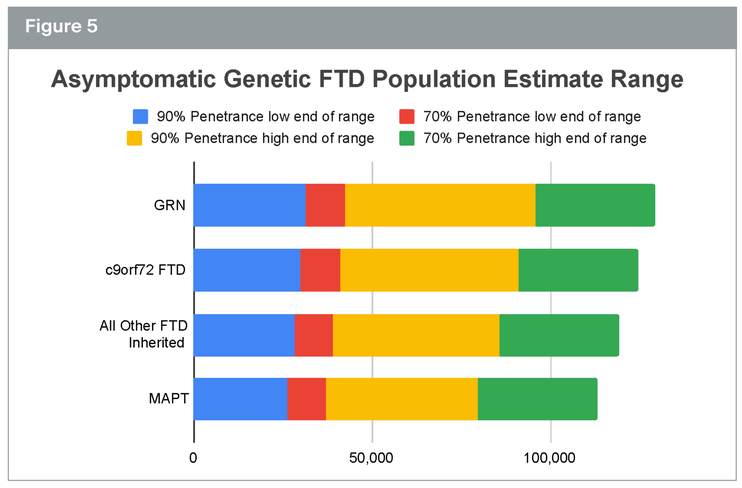


Figure 5



Discussion

- The at-risk genetic community is comprised of multiples of the symptomatic ALS and FTD population.
- Currently, we cannot distinguish between carriers who will undergo phenotypic conversion and those who will remain asymptomatic during life.
- Resources and care contemplated for the genetic community must consider the full asymptomatic population.
- For C9orf72, it is reasonable to assume there will be differing considerations depending on the family history of the disease in line with recent findings[7].
- Available resources should include information and education tailored to the at-risk community, the ability to connect with others in similar positions, and updates on recruiting trials.
- Care considerations for this population include how to allow for monitoring of disease onset and lifestyle advice for those at risk. The first workshop to contemplate these subjects was held on September 21-22 in Pennsylvania.
- Genetic ALS & FTD: End the Legacy is the only patient advocacy group dedicated specifically to the genetic community. As such, we are proud to not only provide resources for our global community but also to serve as engaged community leaders in efforts such as the mentioned workshop, committees convened by research leaders and government, and in discussions with industry.

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