The discovery in 2011 of the C9orf72 repeat expansion clarified the genetic cause of a significant subset of familial and seemingly sporadic Amyotrophic Lateral Sclerosis (ALS) and Frontotemporal Dementia (FTD) cases. Following the discovery, numerous studies have looked into C9orf72, the prevalence of repeat expansion in ALS and FTD cases, and the impact on carriers. As a carrier myself, I realized there were significant issues that concerned me regarding C9orf72, which most treated as a mystery, including how many people carry the expansion? What is the impact on mortality when one has the expansion? How many people can be said to be experiencing the ALS or FTD disease process before diagnosis? Upon reflection, it became clear that by data-mining previously reported results, we could arrive at rough estimates for many of these missing data points. Here, I will describe my calculations, their outcome, and the potential implications for drug development, treatment, support, and related issues arising from these results.

### 3) Results

#### Prevalence Of C9orf72 Carriers in the US

<table>
<thead>
<tr>
<th>Category</th>
<th>Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extensive Data</td>
<td>154,743</td>
</tr>
<tr>
<td>Estimated Total Population of C9orf72 Carriers in the US</td>
<td>46.55 per 100k</td>
</tr>
<tr>
<td>Premanifest ALS and FTD Population</td>
<td>125,454</td>
</tr>
<tr>
<td>Non-Penetrant C9orf72 Population</td>
<td>16,632</td>
</tr>
</tbody>
</table>

#### Premanifest, Non-Penetrant, and C9orf72 Carriers living with an ALS or FTD Diagnosis combined equals 154,743 total C9orf72 carriers in the US or 46.55 per 100k. The At-Risk Population is estimated at 309,486 or 93.1 per 100k.

#### Average Life Expectancy For C9orf72 Carriers

- **Assuming an Equal Distribution between FTD and ALS**
  - 49% of carriers will be diagnosed with ALS and will live on average 69 years.
  - 50% of carriers will be diagnosed with FTD and will live on average 73 years.
  - 1% of carriers will not manifest ALS or FTD and will live on average 78 years.

- **Average weighted age at death** of 69% 69, 49% 73, and 10% 78 equals 74

- **Assuming the greater incidence of C9 ALS is correct**
  - 41% of carriers will be diagnosed with ALS and live on average 69 years.
  - 44% of carriers will be diagnosed with FTD and will live on average 74 years.
  - 5% of carriers will not manifest ALS or FTD and will live on average 78 years.

- **Average weighted age at death** of 40% 69, 44% 74, and 10% 78 equals 73

#### A C9orf72 Carrier’s Life Expectancy is estimated at 64.4 if there is an equal distribution between ALS and FTD cases and 65.6 if the distribution is 25.8% ALS and 64.6% FTD.

#### The population of C9orf72 Carriers Experiencing Pre-Manifest Disease

<table>
<thead>
<tr>
<th>Category</th>
<th>Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carriers living with an ALS or FTD disease length</td>
<td>3 years</td>
</tr>
<tr>
<td>Carriers living with an ALS or FTD disease activity length</td>
<td>7 years</td>
</tr>
</tbody>
</table>

#### The population of C9orf72 Carriers experiencing pre-manifest disease is 68,560 if it is 40 years, 32,445 if it is 15 years, and 6,489 if it is three years.

### 4) Discussion

The population of C9orf72 carriers in the US is large. As most individuals at risk of genetic ALS do not pursue predictive testing, it is only practical to estimate the full population of those at risk for the gene, which is even larger. This is the same size or larger than the population in the US that carry the expansion repeated for Huntington’s disease or are at risk for it.

When considering possible drugs for the treatment or curing of ALS and FTD, we must consider that the population of those who have a compelling reason to be administered treatment or care includes the 60% pre-symptomatic population. Looking past C9orf72, this more than quadruples the number of people with ALS and an diagnosis. Suppose we are to be more conservative and only provide a treatment or care after the disease process has begun. In that case, we can see that it is still a very large population of between 65,520 in an more substantial definition. Keeping in mind this has implications for the market and increases the strategies available for drug development and intervention and multiple stages of the diseases.

Knowing one is a risk of ALS and FTD and likely have a multi-year window to begin. We must consider what resources are available to this pool of potential. Through hard work and compassion, we can see that the Huntington’s Disease Community has amassed many resources for those at risk, led perhaps most ambitiously by the Huntington’s Disease Youth Organization. Those of us at risk of genetic ALS and FTD are anything as well organized. But we have started to address this with the Familial ALS Team at a ALS. However, as we build these support systems, the clinical and impacted communities must work together closely.

Sometimes people attempt to view the situation of a C9orf72 carrier regarding reduced mortality. They lean on the facts in the likely not fully penetrant. We can see that the probability of someone who is a C9orf72 carrier is likely, on average, 12.6 - 11.84 years less than an unaffected person. That means (12.6 - 11.84) * 100 for a male C9orf72 carrier. These are meaningful differences, as it would be prudent and reasonable for a C9orf72 carrier to employ any possible attempt to prevent the worst of the disease.

### Acknowledgements

I am debt to the many dedicated researchers who have worked so hard characterizing the C9orf72 repeat expansion over the years. The many patients who have shared their stories, my late mother and grandmother, who have participated in research, and Bryan Crouch for encouraging the post. Paul Hicks and Jason Perea for their advice. My Familial ALS Team and I ALS for support. And my mother and daughter for being amazing.