**Calculation of EYOs**

**Part I: Three Types of Age of Symptom Onset and the Master Database**

**(I) The Decline Age (or the mean of the decline ages)—Age of symptom onset for individuals who are already symptomatic:** CDR global score (referred to as CDR hereafter) is used to define Symptomatic and Asymptomatic. At each visit, a CDR score will be determined by the clinician. CDR 0 is considered asymptomatic. While CDR 0.5 or above is considered symptomatic. At each visit, if a CDR of 0.5 or above is given by the clinician at study entry, the clinician will determine a *decline age* using standardized list of symptoms to explore the earliest age of symptom onset. This decline age is thereafter defined as age of symptom onset. In very rare cases that a CDR 0.5 or above is determined at a visit but the corresponding decline age is not provided, then the individual’s age at the visit where the 1st CDR of 0.5 or above is given will be used as the decline age (age of symptom onset). The DIAN observational study is designed in a way such that, at each post-baseline visit, the clinician is blinded to an individuals’ data collected in the previous visit/visits to increase the independence and accuracy of evaluation. That means at all the visits where a CDR of 0.5 or above is given, a decline age will also be provided. Therefore, multiple decline ages are typically available for individuals with multiple visits with CDRs of 0.5 or above. In these cases, the mean of these decline ages for each individual will be calculated and used as the age of symptom onset for that individual. Hereafter, we generally refer to this type of age of symptom onset as “**the mean of decline ages”**.

If an individual had a CDR of 0.5 at one visit and a CDR of 0 at the following visit, then the previous CDR 0.5 will be considered as false symptomatic signal and a decline age will not be established until there are consecutive scores of CDR >0 and no further CDR 0 scores.

**(II) Mean Mutation Age of Symptom Onset:** the mean of the onset ages for individuals with the same mutation. A master database has been built by the DIAN observational study team. This database includes almost 4000 unique persons with ADAD and known mutations. Of them, about 1500 had known age of onset, and these ages of onset are used to calculate the mean mutation age of onset.

**(III) Parental or Proxy Age of Symptom Onset:** Individual’s parental age of onset. In the unlikely event that an individual has two parents (consanguinity) that carry the same mutation, then the parental age of onset will be the mean of both parents’ onset ages. In the event a Parental age of onset cannot be determined, the closest relative with an age of onset will be used as a proxy for age of symptom onset.

**The Master Database**: The master database will be updated so that any recently discovered new mutations, additional individuals with established mutations, or updated ages of onset for those already in the database can be included. Once the database is updated, the mean mutation age of symptom onset or parental age of symptom onset will be re-calculated to increase accuracy. Although the parental age of onset typically does not require any calculation since in most cases only one parental age of onset is available. Subsequently, the estimated years from symptom onset (EYO) will also be re-calculated. That means the EYOs of the same person may change due to the updating of the master database. Therefore, the same person’s EYOs at the same visits, say, in Data Freeze 07, can be different from those in Data Freeze 12.

It is anticipated that the master database will be updated every 3-4 years. Before a new update, all the data freeze will use the same mean mutation age of symptom onset and thus leads to the same EYOs for the same visits of the same person.

**Part II: Mutation/Parental EYO**

**Mutation/Parental EYO calculation (Names as dian\_mutpar\_eyo in DF11)**: This EYO is calculated based on (1) mean mutation age of symptom onset and (2) parental age of symptom onset in the following ordered steps (applied to both mutation carriers and non-carriers):

(i) At any visit, EYO equals to the visit age minus the mean mutation age of symptom onset (EYO=Visit age – Mean mutation age of symptom onset) if the individual’s mutation is known and the mean mutation age of symptom onset for this individual’s mutation is available in the master database.

(ii) If any given individual’s mutation is not available in the master database (e.g. the mutation has not been previously reported or other member age of onset not available) then at any visit, EYO equals to the visit age minus the parental age of symptom onset (EYO=Visit age – parental age of symptom onset).

Every DIAN participant has at least one of these two pieces of information, thus every participant will have this type of EYO values.

**Part III: DIAN EYO**

**DIAN EYO (named as DIAN\_EYO in DF11)**: The DIAN EYO improves the accuracy of the EYO estimation by incorporating an individual’s actual decline age in determining their EYO as opposed to just using the mean mutation or parental age of symptom onset.

**DIAN EYO Calculation** (applied to both mutation carriers and non-carriers)**:**

(i) For symptomatic individuals with reported decline ages, their DIAN EYO= Visit age – the mean of decline ages.

(ii) For asymptomatic individuals, their DIAN EYO = their Mutation/Parental EYO.

**DIAN EYO is dynamic and will be updated for each data freeze to reflect individual’s symptomatic status change during follow-up.**