Estimation of the Prevalence of PTEN Hamartoma Tumour Syndrome and Opportunities for Orphan Drug Designation

PTEN Hamartoma Tumour Syndrome (PHTS) is a rare syndrome caused by germline heterozygous loss-of-function mutation in the Phosphatase and Tensin Homolog (*PTEN*) tumour suppressor gene. Before the identification of the PTEN gene and routine genetic testing of patients with rare congenital conditions, several syndromes were described based on clinical features including Cowden syndrome (CS), Bannayan–Riley–Ruvalcaba syndrome (BRRS), Proteus syndrome (PS) and Proteus-like syndrome.

Estimation of the prevalence of PHTS and its associated conditions is complex in part due to the variability of phenotypic and genotypic presentation of patients. Additionally, several of the features of PHTS are relatively common in the general population, including benign lesions of the breast and uterus and as such patients may not have been recognized as having PHTS. This means that the incidence of PHTS in the general population may be higher than estimated[1].

Further, given that a diagnosis of PHTS is defined genetically, biases in PHTS prevalence are likely to exist based on access to genetic testing. Therefore, the prevalence estimates presented below represent clinical syndromes associated with a PHTS-like phenotype as a best currently available estimate.

Cowden Syndrome (CS)

Consensus clinical diagnostic criteria for CS have been developed and are updated each year by the National Comprehensive Cancer Network (NCCN)[2]. Approximately 25-85% of patients meeting these criteria also express an identified PTEN gene germline mutation[3].

Few formal epidemiological studies have been published. Nelen and colleagues[4] have estimated that the prevalence of CS in the Dutch population is between 1 in 200,000 and 1 in 250,000 based on a database of > 4.5 million individuals. The authors also highlight the possibility of misdiagnosis. Given the phenotypic variability of CS, the above may represent an underestimate.

MedlinePlus, maintained under the auspices of the US National Library of Medicine and the NIH and the European Union supported Orphanet both list that the exact prevalence of Cowden syndrome is unknown, but it is estimated that it affects about 1 in 200,000 individuals[5,6], but it is noted that the condition is likely underdiagnosed[2].

Bannayan–Riley–Ruvalcaba syndrome (BRRS)

At present no formal consensus criteria exist for the diagnosis of BRRS[2]. Approximately 60% of BRRS patients have identified PTEN germline mutations[3].

The prevalence of is unknown[7,8] although it appears to be rare. Several dozen cases have been reported in the medical literature. As with CS, the disorder is likely to be underdiagnosed due to the variability of patients and lack of formal consensus diagnostic criteria.

Proteus syndrome (PS) and Proteus-like syndrome

Proteus syndrome (PS) is an extremely rare and highly variable condition and affects individuals in a mosaic distribution. Thus, it is frequently misdiagnosed despite the development of consensus

clinical diagnostic criteria[2]. Proteus-like syndrome is undefined[2] but describes individuals with significant clinical features of PS but who do not meet the diagnostic criteria. It is estimated that between 7-67% of PS and Proteus-like syndrom patients have identified PTEN germline mutations[3].

The prevalence of Proteus syndrome is estimated as less than 1 in 1 million individuals worldwide. Only a limited number of affected individuals have been reported in the medical literature[9,10].

French National Database of Rare Diseases

Currently, few sources contain systematic population level data about the prevalence of PHTS or associated clinical syndromes. One such source is the French National Database of Rare Diseases (BNDMR), where a report dated May 2024 detailed at least 628 living patients as having PHTS (n=57) or the clinical diagnoses of CS (n=531), BRRS (n=39) or Proteus-like syndrome (n≤10) corresponding to a combined prevalence of approximately 1:108,000[11].

Orphan Drug Designation Criteria

United States[12]

Within the US, to meet the criteria of the Orphan Drug Act of January 1983 (ODA) for Orphan Drug Designations, the molecule under assessment must be indicated for the prevention, diagnosis or treatment of diseases or conditions affecting fewer than 200,000 persons in the US. **It is noted that this designation is given to a drug for a disease or condition and not granted to the indication.** (There are additional criteria for drugs that will not be profitable within 7 years following approval by the FDA.)

In the context of PHTS:

- The maximum reported prevalence for a PHTS subset is Cowden Syndrome with an estimated prevalence in the literature of 1 in 200,000.
- On this basis, the estimated PHTS patient population in the US: the current US population[13]/ disease prevalence = 336,600,000/200,000 c. 1,683 individuals.
- The following limitations should be noted:
    - the estimated prevalence of 1 in 200,000 is based on a single epidemiological study of CS undertaken in a Dutch patient population[4];
    - this may be an underestimate as several CS/PHTS features are quite common in the general population leading to under-diagnosis;
    - it is clearly a gross simplification to extrapolate the prevalence of the whole PHTS population from as single estimation of CS prevalence. It excludes individuals with BRRS and PS/Proteus-like syndrome but includes individuals with a clinical diagnosis of CS not all of whom will express an identified PTEN gene germline mutation.
- Despite these caveats, even if the prevalence was subject to a 100-fold increase, PHTS would still meet the US criteria for orphan drug designation.

European Union[14,15]

The Committee for Orphan Medicinal Products (COMP) is the European Medicines Agency's (EMA) committee responsible for recommending orphan designation of medicines for rare diseases. The COMP was established in 2000, in line with Regulation (EC) No 141/2000.

To qualify for orphan designation, a medicine must meet several criteria:

- it must be intended for the treatment, prevention or diagnosis of a disease that is life-threatening or chronically debilitating;
- the prevalence of the condition in the EU must not be more than 5 in 10,000 or it must be unlikely that marketing of the medicine would generate sufficient returns to justify the investment needed for its development;
- no satisfactory method of diagnosis, prevention or treatment of the condition concerned can be authorised, or, if such a method exists, the medicine must be of significant benefit to those affected by the condition.

On the basis of the COMP criteria and the available prevalence data on CS (despite the qualifications noted above) it may be inferred that a drug being developed to treat any or all PHTS subsets could meet the definition for orphan designation within the EU. It is noted that all PHTS subsets may be considered life-threatening or chronically debilitating and the lack of existing therapeutic interventions currently available would also support orphan designation in the EU.

Discussion and Further Activity

The currently available published prevalence data for PHTS is limited. This is also complicated given i) not all the clinical conditions associated with PHTS have formal consensus diagnostic criteria and ii) where consensus diagnostic criteria do exist, not all patients meeting the clinical criteria also express an identified PTEN germline mutation.

However, despite this, the limited prevalence data available would indicate that a molecule developed for the treatment of PHTS would likely meet the criteria for orphan drug designation in both the US and EU. It should also be noted that a marketing approval would be almost certainly limited to the PHTS patient subpopulation studied in the pivotal trial(s) and not the entire PHTS patient population which would further reduce the patient population considered in the context of an orphan drug designation application.

Consultation with a Regulatory Affairs professional would be advisable to validate the above assessment and to gain insights into recent Health Authority precedents for other orphan drug designations.

Regardless, a better understanding of PHTS prevalence would be valuable to support not only future Health Authority interactions and potential orphan drug designation applications but also to guide future drug development efforts and assessment of the burden of PHTS on payors and healthcare systems.

The Foundation is also aware that a European expert centre is undertaking an effort to better estimate PHTS prevalence. Whilst this activity is not directly supported by the Foundation, we understand the publication is expected shortly.

It is also intriguing to extrapolate the potential PHTS prevalence based on other literature sources. For instance:

- It is estimated that autism spectrum disorder (ASD) affects approximately 2.2% of adults in the United States[16], and 1% of individuals in Europe[17].
- Further, estimates suggest that~15% of ASD cases have macrocephaly defined as >2 SDs per age norms[18].
- A meta-analysis of 9 studies indicated approximately 17% of macrocephalic ASD patients also had PTEN germline mutation[19].
- In the light of last two findings, Frazier has suggested approximately 2% of all individuals with ASD will also have a PTEN germline mutation[20].

On this basis the prevalence of PHTS with ASD may be estimated to be as high as 4 patients in 10,000 in the US and 2 patients per 10,000 in the EU. However, the lack of formal statistical analyses in deriving this estimate, and likely ascertainment biases in the source datasets, must be underlined. (Also noteworthy is that in a recent large study with sequencing data from 5100 individuals with ASD, PTEN was one of the most common genes with ASD associated rare variants[21].) Even with this estimation it is still expected that any drug developed for PHTS would fulfil the criteria for an orphan drug designation in both the US and European Union.

Other potential ways to obtain enhanced estimates on PHTS prevalence would include interrogating anonymised electronic medical records (EMR) or health care provider's claims data. Commercial organisations such as TriNetX can provide access to databases extracted from health care systems in several countries including the US. It should be noted that the applicable ICD-10-CM and ICD-11 codes were only implemented for PHTS in late 2022 and early 2023, respectively, and therefore the lack of appropriate coding in affected individual's electronic medical records is likely to hamper accurate prevalence estimations for several years.

The use of data from biobanks may also be worth exploring. As an example, the UK Biobank includes samples from 500,000 individuals that have been genotyped with a plan for full genome sequencing of 50,000 samples. However, given the current estimated disease prevalence, the overall number of samples within a biobank would have to be significantly greater to provide meaningful data.

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