

Additional file 1: selection criteria for the TREAT-panel

1. TREATability

Scoring	Definition
YES	Approved drug treatment (EMA) incl. gene therapy and/or other treatment/intervention (drug, diet, bone marrow transplantation, supplements, vitamins, etc) that is recommended by guidelines (at least for a subgroup of the disease) and Treatment available in Germany and Italy
NO	All genes/diseases not fulfilling the criteria above ☒ Leads to immediate exclusion

2. Disease onset

Scoring	Definition
2	Predominantly paediatric onset of disease
1	Spectrum of onset across age groups, difficult to predict onset/limited knowledge about natural history of disease
0=NO	Mainly adult onset (> 18 years) ☒ Leads to immediate exclusion

Subcriterion: Treatment needed within the first two years of life.

3. Disease severity

Scoring	Definition
2	Most likely to cause significant health problem
1	Spectrum of severity, difficult to predict
0	Not causing significant health problem

4. Penetrance

Scoring	Definition
2	Penetrance > 80%
1	Intermediate penetrance (20-80%)
0	Low penetrance (< 20%)

5. Clinical validity

Scoring	Definition
2	known pathogenic variants with clear phenotype-genotype correlation
1	genes with known pathogenic variants and partial genotype/phenotype correlation (as in ultrarare conditions)
0	genes with only benign variants or variants of unknown significance, no established genotype-phenotype correlation

6. Genetic feasibility

Scoring	Definition
YES	significant number of pathogenic variants annotated in database, detectable by our comprehensive NGS approach

NO	Non-mendelian inheritance, not identifiable by chosen NGS Approach ☒ Leads to immediate exclusion
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