Case Definitions for Aggregate Case Entry

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INTRODUCTION

NewSTEPs collects aggregate case data, representing the total number of confirmed cases for each newborn screening (NBS) disorder by birth year. This data is used to determine the birth prevalence of each disorder detected by newborn screening for each state/territory (see Quality Indicator 7). NBS Programs are requested to submit aggregate cases for the Core Recommended Uniform Screening Panel (RUSP) disorders, with the option to enter aggregate cases for Secondary RUSP disorders. Data collection follows a two-year delay (e.g., cases for infants born in 2023 are submitted in 2025) to allow sufficient time for case closure.

Unlike the individual case data, which collects demographic, screening, and follow-up information, aggregate case counts serve as the official annual totals of disorders identified through newborn screening. Individual cases may include non-core RUSP conditions (e.g., CFTR-related metabolic syndrome or benign hyperphenylalaninemia) to help evaluate the public health impact of NBS. However, aggregate case counts should only include the Core RUSP disorder (e.g., typical cystic fibrosis and classical phenylketonuria). **Please use this guide to determine what core disorders should be counted in the aggregate cases for NewSTEPs**. Only cases for disorders included in the program's routine screening panel during the birth year should be reported.

For step-by-step guidance on entering case data, refer to pages 25-27 of the NewSTEPs User Guide.

ORGANIC ACID DISORDERS

3-Hydroxy-3-Methylglutaric Aciduria (HMG)—Elevated C5-OH

- **Case Definition**: Infant confirmed with 3-hydroxy-3-methylglutaric aciduria through diagnostic testing.
- Do not count these other clinically relevant diseases in the aggregate case count for 3-hydroxy-3-methylglutaric aciduria:
    - 2-methyl-3-hydroxybutyric acidemia (MHBD or 2M3HBA)
    - 3-methylglutaconic aciduria (MGA or 3MGA)
        - *Note: 2M3HBA and 3MGA are counted separately in the aggregate case collection, but not as the Core RUSP disorder.*
    - Biotinidase deficiency
    - Maternal 3-MCC
    - MT-ATP6-related mitochondrial disorders

3-Methylcrotonyl-CoA Carboxylase Deficiency (3-MCC)—Elevated C5-OH

- **Case Definition**: Infant confirmed with 3-methylcrotonyl-CoA carboxylase deficiency through diagnostic testing.
- Do not count these other clinically relevant diseases in the aggregate case count for 3-methylcrotonyl-CoA carboxylase deficiency:
    - 2-methyl-3-hydroxybutyric acidemia (MHBD or 2M3HBA)
    - 3-methylglutaconic aciduria (MGA or 3MGA)
        - *Note: 2M3HBA and 3MGA are counted separately in the aggregate case collection, but not as the Core RUSP disorder.*
    - Biotinidase deficiency
    - Maternal 3-MCC
    - MT-ATP6-related mitochondrial disorders

B-Ketothiolase Deficiency (BKT)—Elevated C5-OH

- **Case Definition**: Infant confirmed with β-kethothiolase deficiency through diagnostic testing.
- Do not count the other clinically relevant diseases in the aggregate case count for β-kethothiolase deficiency:
    - 2-methyl-3-hydroxybutyric acidemia (MHBD or 2M3HBA)
    - 3-methylglutaconic aciduria (MGA or 3MGA)
        - *Note: 2M3HBA and 3MGA are counted separately in the aggregate case collection, but not as the Core RUSP disorder.*
    - Biotinidase deficiency
    - Maternal 3-MCC
    - MT-ATP6-related mitochondrial disorders

Holocarboxylase Synthase Deficiency (MCD)—Elevated C5-OH

- **Case Definition**: Infant confirmed with holocarboxylase synthase deficiency through diagnostic testing.
- Do not count these other clinically relevant diseases in the aggregate case count for holocarboxylase synthase deficiency:
    - 2-methyl-3-hydroxybutyric acidemia (MHBD or 2M3HBA)
    - 3-methylglutaconic aciduria (MGA or 3MGA)
        - *Note: 2M3HBA and 3MGA are counted separately in the aggregate case collection, but not as the Core RUSP disorder.*
    - Biotinidase deficiency
    - Maternal 3-MCC
    - MT-ATP6-related mitochondrial disorders

Glutaric Acidemia Type I (GA I)

- **Case Definition**: Infant confirmed with glutaric acidemia type I through diagnostic testing.

Isovaleric Acidemia (IVA)

- **Case Definition:** Infant confirmed with isovaleric acidemia through diagnostic testing.
- Do not count these other clinically relevant diseases in the aggregate case count for isovaleric acidemia:
    - 2-Methylbutyrylglycinuria (2MBG)
    - Glutaric acidemia type II (GA II)/ Multiple acyl-CoA dehydrogenase (MAD deficiency)
    - Short/branched chain acyl-CoA dehydrogenase (SBCAD) deficiency
        - *Note: 2MBG, GA II, and SBCAD are counted separately in the aggregate case collection, but not as the Core RUSP disorder.*

Methylmalonic Acidemia (methylmalonyl-CoA mutase)—Elevated C3

- **Case Definition:** Infant confirmed with methylmalonic acidemia (methylmalonyl-CoA mutase) through diagnostic testing.
- Do not count these other clinically relevant diseases in the aggregate case count for methylmalonic acidemia (methylmalonyl-CoA mutase):
    - Methylmalonyl-coenzyme A epimerase (MCEE) deficiency
    - Partially deficient or B_{12}-responsive phenotypes
    - Cbl C, Cbl D

        - *Note*: *These cobalamin deficiencies are counted under methylmalonic acidemia with homocystinuria- Cbl C,D in the aggregate case collection, but not as the Core RUSP disorder.*
    - Results consistent with Cbl F, CblJ, Cbl X, Cbl TC-II
    - Succinate-CoA ligase deficiency
    - Transcobalamin receptor deficiency

Methylmalonic Acidemia (Cbl A,B)—Elevated C3

- **Case Definition:** Infant confirmed with methylmalonic acidemia (cobalamin disorders Cbl A,B) through diagnostic testing.
- Do not count these other clinically relevant diseases in the aggregate case count for methylmalonic acidemia (cobalamin disorders Cbl A,B):
    - Methylmalonyl-coenzyme A epimerase (MCEE) deficiency
    - Partially deficient or B_{12}-responsive phenotypes
    - Cbl C, Cbl D
        - *Note: These cobalamin deficiencies are counted under methylmalonic acidemia with homocystinuria- Cbl C,D in the aggregate case collection, but not as the Core RUSP disorder.*
    - Results consistent with Cbl F, CblJ, Cbl X, Cbl TC-II
    - Succinate-CoA ligase deficiency
    - Transcobalamin receptor deficiency

Propionic Acidemia (PROP)—Elevated C3

- **Case Definition:** Infant confirmed with propionic acidemia through diagnostic testing.
- Do not count these other clinically relevant diseases in the aggregate case count for propionic acidemia:
    - Methylmalonyl-coenzyme A epimerase (MCEE) deficiency
    - Partially deficient or B_{12}-responsive phenotypes
    - Results consistent with Cbl C, Cbl D
        - *Note: These cobalamin deficiencies are counted under methylmalonic acidemia with homocystinuria- Cbl C,D in the aggregate case collection, but not as the Core RUSP disorder.*
    - Results consistent with Cbl F, CblJ, Cbl X, Cbl TC-II
    - Succinate-CoA ligase deficiency
    - Transcobalamin receptor deficiency

FATTY ACID OXIDATION DISORDERS

Carnitine Uptake/Transport Defect (CUD)

- **Case Definition:** Infant confirmed with carnitine uptake/transport defect through diagnostic testing.
- Do not count these other clinically relevant diseases in the aggregate case count for carnitine uptake/transport defect:
    - Maternal carnitine deficiency
    - Other fatty acid oxidation defects
    - Other organic acidurias

Medium-Chain Acyl-CoA Dehydrogenase Deficiency (MCAD)

- **Case Definition:** Infant confirmed with medium-chain acyl-CoA dehydrogenase deficiency through diagnostic testing.
- Do not count these other clinically relevant diseases in the aggregate case count for medium-chain acyl-CoA dehydrogenase deficiency:
    - Glutaric acidemia type II (GA II)/ Multiple acyl-CoA dehydrogenase (MAD deficiency)
    - Medium-chain ketoacyl-CoA thiolase deficiency (MCKAT)
        - *Note: GA II and MCKAT are counted separately in the aggregate case collection, but not as the Core RUSP disorder.*

Long-chain L-3 Hydroxyacyl-Co-A Dehydrogenase Deficiency (LCHAD)—Elevated C16-OH +/- C18-OH

- **Case Definition:** Infant confirmed with long-chain L-3 hydroxyacyl-CoA dehydrogenase deficiency through diagnostic testing.
- Do not count these other clinically relevant diseases in the aggregate case count for long-chain L-3 hydroxyacyl-CoA dehydrogenase deficiency:
    - Carnitine palmitoyltransferase type II deficiency (CPT II)
    - Carnitine-acylcarnitine translocase deficiency (CACT)
        - *Note: CPT II and CACT are counted separately in the aggregate case collection, but not as the Core RUSP disorder.*

Trifunctional Protein Deficiency (TFP)—Elevated C16-OH +/- C18-OH

- **Case Definition:** Infant confirmed with trifunctional protein deficiency through diagnostic testing.
- Do not count these other clinically relevant diseases in the aggregate case count for trifunctional protein deficiency:

    - Carnitine palmitoyltransferase type II deficiency (CPT II)
    - Carnitine-acylcarnitine translocase deficiency (CACT)
        - *Note: CPT II and CACT are counted separately in the aggregate case collection, but not as the Core RUSP disorder.*

Very Long-Chain Acyl-CoA Dehydrogenase Deficiency (VLCAD)

- **Case Definition:** Infant confirmed with very long-chain acyl-CoA dehydrogenase deficiency through diagnostic testing.
- Do not count these other clinically relevant diseases in the aggregate case count for very long-chain acyl-CoA dehyrdrogenace deficiency:
    - Carnitine palmitoyltransferase type II deficiency (CPT II)
    - Carnitine-acylcarnitine translocase deficiency (CACT)
        - *Note: CPT II and CACT are counted separately in the aggregate case collection, but not as the Core RUSP disorder.*

AMINO ACID DISORDERS

Argininosuccinic Aciduria (ASA)—Elevated Citrulline

- **Case Definition:** Infant confirmed with argininosuccinic aciduria through diagnostic testing.
- Do not count these other clinically relevant diseases in the aggregate case count for argininosuccinic aciduria:
    - Citrullinemia type II (CIT II)
    - Ornithine transcarbamylase deficiency (OTC)
        - *Note: CIT II and OTC are counted separately in the aggregate case collection, but not as the Core RUSP disorder.*
    - Pyruvate carboxylase deficiency

Citrullinemia Type I (CIT)—Elevated Citrulline

- **Case Definition:** Infant confirmed with citrullinemia type I through diagnostic testing.
- Do not count these other clinically relevant diseases in the aggregate case count for citrullinemia type I:
    - Pyruvate carboxylase deficiency
    - Citrullinemia type II (CIT II)
    - Ornithine transcarbamylase deficiency (OTC)
        - *Note: CIT II and OTC are counted separately in the aggregate case collection, but not as the core RUSP disorder.*

Classic Phenylketonuria (PKU)

- **Case Definition:** Infant confirmed with classic phenylketonuria (PKU, PAH deficiency) through diagnostic testing.
    - *Note: The dropdown menu says "Classic PKU and Hyperphe" but for aggregate case count, this should only include classic PKU.*
- Do not count these other clinically relevant diseases in the aggregate case count for classic phenylketonuria (PKU, PAH deficiency):
    - Benign hyperphenylalaninemia
    - Biopterin cofactor defects
    - Dihydropteridine reductase deficiency (DHPR)
    - *DNAJC12* disease
    - HyperPhe Diet Controlled
    - Maternal PKU
    - Transient hyperphenylalaninemia

Homocystinuria (HCY)

- **Case Definition:** Infant confirmed with homocystinuria through diagnostic testing.
- Do not count these other clinically relevant diseases in the aggregate case count for homocystinuria:
    - Adenosylhomocysteine hydrolase deficiency
    - Glycine n-methyltransferase (GNMT) deficiency
    - Hypermethioninemia (MET)
        - *Note: MET is counted separately in the aggregate case collection, but not as the Core RUSP disorder.*
    - Methionine adenosyltransferase (MAT) I/III deficiency

Maple Syrup Urine Disease (MSUD)

- **Case Definition:** Infant confirmed with maple syrup urine disease through diagnostic testing. This includes classic, intermediate, intermittent, thiamine-response, and unclassified.
- Do not count Hydroxyprolinemia in the aggregate case count for maple syrup urine disease.

Tyrosinemia Type I (TYR I)

- **Case Definition:** Infant confirmed with tyrosinemia type I through diagnostic testing.
- Do not count these other clinically relevant diseases in the aggregate case count for tyrosinemia type I:
    - Transient tyrosinemia of the newborn
    - Tyrosinemia, type II (TYR II)
    - Tyrosinemia, type III (TYR III)

- *Note: TYR II and TYR III are counted separately in the aggregate case collection, but not as the Core RUSP disorder.*

ENDOCRINE DISORDERS

Congenital Adrenal Hyperplasia (CAH)

- **Case Definition:** Infant confirmed with classic congenital adrenal hyperplasia (salt-wasting or simple virilizing) caused by 21-hydroxylase deficiency through diagnostic testing.
- Do not count these other clinically relevant diseases in the aggregate case count for congenital adrenal hyperplasia:
  - CAH caused by 11-beta-hydroxylase deficiency
  - CAH caused by other deficiencies
  - Cytochrome P450 oxidoreductase deficiency
  - Non-classic CAH

Primary Congenital Hypothyroidism (CH)

- **Case Definition:** Infant confirmed with primary congenital hypothyroidism through diagnostic testing. For the purpose of this data collection, a case is considered confirmed even if a three-year challenge has not been completed.
- Do not count these other clinically relevant diseases in the aggregate case count for primary congenital hypothyroidism:
  - Secondary/central congenital hypothyroidism
  - Subclinical hypothyroidism
  - Tertiary hypothyroidism
  - Transient CH cases
  - Thyroxine binding globulin (TBG) deficiency

HEMOGLOBIN DISORDERS

Presence of Hemoglobin S (S, Beta-Thalassemia, S,C disease, and Sickle Cell Anemia)

- **Case Definition:** Infant confirmed with sickle cell anemia (S, S disease or S, βeta Zero (β0) Thalassemia), S, βeta plus thalassemia, or S,C disease by diagnostic hemoglobin electrophoresis or molecular testing. This result can be in combination with alpha (Barts) variants.
- Do not count these other clinically relevant diseases in the aggregate case count for Presence of Hb S:
  - Hemoglobin S /Hereditary Persistence of Fetal Hemoglobin (HPFH)
  - Sickling or Hgb trait (i.e., FAC, FAS, ACF, ASF, AC, AS, AFC, AFS) with or without Barts
  - Various other hemoglobinopathies

- *Note: Hemoglobin C, D, E, O-Arab Disease, and other hemoglobin disorders (e.g., Hemoglobin C/beta plus thalassemia, Hemoglobin C/beta zero thalassemia, Hemoglobin E/beta zero thalassemia, etc.) should be entered under **Presence of Other Hb Variant**.*
- *Alpha Thalassemia Major (Fetal Hydrops), Beta Thalassemia Major (Cooly's Anemia), and Hgb H disease should be entered under **Hb-No Structural Variant**.*

LYSOSOMAL STORAGE DISORDERS

Infantile Krabbe (Krabbe)

- **Case Definition:** Infant confirmed with infantile Krabbe through diagnostic molecular testing. If molecular confirmation predicts infantile Krabbe, classify as a confirmed case even in the absence of an overt clinical presentation.
- Do not count cases of pseudodeficiency or if the diagnostic testing remains inconclusive, including variants of unknown significance (VUS).
- Do not count Saposin A deficiency for infantile Krabbe disease.
- Do not count predicted later-onset Krabbe disease

Glycogen Storage Disease Type II (Pompe)

- **Case Definition:** Infant confirmed with infantile or later-onset Pompe through diagnostic molecular testing. If molecular confirmation predicts Pompe, classify as a confirmed case even in the absence of an overt clinical presentation (i.e., infant may not have cardiomyopathy).
    - *Note: determination of later-onset cases is associated with the absence of early clinical symptoms and the presence of pathogenic variants.*
- Do not count cases of pseudodeficiency or if the diagnostic testing remains inconclusive, including variants of unknown significance (VUS).

Metachromatic Leukodystrophy (MLD)

- **Case Definition:** Infant confirmed with metachromatic leukodystrophy through diagnostic testing. If molecular confirmation determines MLD, classify as a confirmed case even in the absence of clinical presentation.
- Do not count cases of pseudodeficiency or if the diagnostic testing remains inconclusive, including variants of unknown significance (VUS).
    - Do not count these other clinically relevant diseases in the aggregate case count of metachromatic leukodystrophy:
    - Multiple sulfatase deficiency
    - Saposin B-deficient MLD

Mucopolysaccharidosis Type I (MPS I)

- **Case Definition:** Infant confirmed with attenuated or severe mucopolysaccharidosis type I through diagnostic testing. If molecular confirmation determines MPS I, classify as a confirmed case even in the absence of clinical presentation.
    - *Note: determination of later-onset cases may be associated with the absence of early clinical symptoms and the presence of pathogenic or likely pathogenic variants.*
- Do not count cases if the diagnostic testing remains inconclusive, including variants of unknown significance (VUS).

Mucopolysaccharidosis Type II (MPS II)

- **Case Definition:** Infant confirmed with attenuated or severe mucopolysaccharidosis type II through diagnostic testing. If molecular confirmation determines MPS II, classify as a confirmed case even in the absence of overt clinical presentation.
    - *Note: determination of later-onset cases may be associated with the absence of early clinical symptoms and the presence of pathogenic or likely pathogenic variants.*
- Do not count cases if the diagnostic testing remains inconclusive, including variants of unknown significance (VUS)
- Do not count Multiple Sulfatase Deficiency for MPS II.

OTHER DISORDERS

Biotinidase Deficiency (BIOT)

- **Case Definition:** Infant confirmed with profound biotinidase deficiency through diagnostic testing.
- Do not count partial biotinidase deficiency in the aggregate case count for BIOT.

Cystic Fibrosis (CF)

- **Case Definition:** Infant confirmed with typical cystic fibrosis through sweat test and/or diagnostic testing.
- Do not count Cystic fibrosis transmembrane conductance regulator (CFTR)-related metabolic syndrome/ CF screen positive, inconclusive diagnosis (CFSPID) in the aggregate case count for typical cystic fibrosis.

Duchenne Muscular Dystrophy (DMD)

- Case definition: Biological male confirmed with Duchenne muscular dystrophy through molecular diagnostic testing.
- Do not count these other clinically relevant diseases in the aggregate case count for Duchenne muscular dystrophy:
    - Becker muscular dystrophy (BMD)
    - DMD-associated dilated cardiomyopathy (DMD-associated DCM)
    - Heterozygous *DMD* pathogenic (or likely pathogenic) variant in a biologic female
    - Other attenuated dystrophinopathies
    - Other neuromuscular dystrophinopathies
    - Further, do not count as a confirmed case for DMD if:
        - No molecular confirmation of a pathogenic or likely pathogenic *DMD* gene variant in a biologic male
        - Variant of unknown significance (VUS) finding only in absence of other pathogenic or likely pathogenic variant finding

Galactosemia (GALT)

- **Case Definition:** Infant confirmed with classic galactosemia through diagnostic testing.
- Do not count these other clinically relevant diseases in the aggregate case count for classic galactosemia:
    - Congenital portosystemic shunt
    - Duarte galactosemia
    - Epimerase deficiency (GALE)
    - G6PD
    - Kinase deficiency (GALK)
        - *Note: GALE and GALK are counted separately in the aggregate case collection, but not as the Core RUSP disorder.*
    - Mutarotase deficiency (GALM)

Guanidinoacetate methyltransferase (GAMT)

- **Case Definition:** Infant confirmed with guanidinoacetate methyltransferase deficiency through diagnostic testing.

Severe Combined Immunodeficiencies (SCID)

- **Case Definition:** Infant confirmed with leaky or typical severe combined immunodeficiencies through diagnostic testing.
    - *Note: ADA-SCID should be counted as typical SCID and included in case counts (see PIDTC 2022).*
- Do not count these other clinically relevant diseases in the aggregate case count for severe combined immune deficiencies:

- Idiopathic T-cell lymphopenia (i.e., persistent TLC with known etiology)
- Recognized genetic syndromes associated with T-cell lymphopenia (TLC) are counted separately in the aggregate case collection, but not as the Core RUSP disorder
    - DiGeorge (22q11)
    - Ataxia telangiectasia (Louis-Bar syndrome),
    - cartilage hair hypoplasia
    - CHARGE
    - CLOVES
    - Down syndrome,
    - Jacobsen syndrome
    - Nijmegen breakage
    - Noonan
    - TAR + Trisomy 18
    - VACTERL
    - Wiskott-Aldrich syndrome
    - Other medical conditions (e.g., chylothorax, heart defect, impaired thymus, etc.)
        - *Note: these disorders (i.e., DiGeorge, ataxia telangiectasia, etc.) are counted separately in the aggregate case collection as T-cell related lymphocyte deficiencies.*

Spinal Muscular Atrophy (SMA)

- **Case Definition:** Infant confirmed with spinal muscular atrophy through diagnostic molecular testing with any number of *SMN2* copy numbers.
- Do not count non-exon 7 deletion for SMA.

X-Linked Adrenoleukodystrophy (X-ALD)

- **Case Definition:** Infant confirmed with X-linked adrenoleukodystrophy (X-ALD) through diagnostic molecular testing. This includes female X-ALD heterozygotes. A case is considered confirmed when a hemizygous *ABCD1* pathogenic (or likely pathogenic) variant in a biologic male or a heterozygous *ABCD1* pathogenic (or likely pathogenic) variant in a biologic female is identified, even in the absence of clinical symptom onset.
    - *Note: determination of later-onset cases is associated with the absence of early clinical symptoms and the presence of pathogenic variants.*
- Do not count these other clinically relevant diseases in the aggregate case count for X-linked adrenoleukodystrophy:
    - Aicardi-Goutieres disease
    - Other peroxisomal spectrum disorders
    - Zellweger spectrum disorder
        - *Note: Zellweger spectrum disorder is counted separately in the aggregate case collection, but not as the Core RUSP disorder.*
- Further, do not count as a confirmed case for XALD if:

- No molecular confirmation of a pathogenic or likely pathogenic *ABCD1* variant (biologic male or female)
- Variant of unknown significance (VUS) finding only in absence of other pathogenic or likely pathogenic variant finding