

# Inborn errors

## Guide to the completion of the EBMT data collection form: Inborn\_Errors\_v2.2

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**EBMT Registry**

EBMT Clinical Research & Registry Department



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## Introduction

Please make sure you have already checked the **Introduction to the EBMT Registry Completion Guidelines** document latest version available under *Manuals and Reference Documents* section on [EBMT website](#).

## Inborn Errors

Inborn errors (inherited disorders) are a group of congenital diseases caused in whole or in part by a change in the DNA sequence away from the normal sequence. Inborn errors can be caused by a mutation in one gene (monogenic disorder), by mutations in multiple genes (oligogenic disorder), or by structural or numerical aberrations of chromosomes.

This form must be completed for all patients whose primary disease for which the reported treatment is being given is an Inborn Error.

No data items should be left blank unless specifically stated in the definition.

### Date of diagnosis

Report the date of the first diagnosis of the disease, either clinical or genetic. Add the date when the sample was collected for examination or (in its absence) the date indicated by a physician within the patient's medical record.

### Inborn errors Classification

Select the sub-classification that is appropriate for the Inborn Error and check the box next to it.

**Inborn errors of immunity (IEI)** – a group of inherited disorders caused by mutations in single or multiple genes that result in the specific impairment of normal immune development and function. The clinical presentation of IEI is variable and includes severe or unusual infections, autoimmune diseases, autoinflammation, and malignancies.

**Inborn errors of metabolism** – a group of inherited disorders caused by mutations in genes coding for proteins that function in metabolism.

**Other inborn errors** – a group of inherited disorders that do not fall into any of the above-mentioned categories.

## Is the patient registered in another registry

Answer **No** if the patient is not registered in any other registry except EBMT Registry.

Answer **Yes** if the patient is registered in any other than EBMT registry and specify if the patient is registered in:

- **ESID**, provide also **Patient registry number**; or
- **Other registry**, specify the registry name in the textfield and indicate the **Patient registry number**.

## Inborn Errors of Immunity (IEI)

### Specify the gene in which a disease-causing variant was observed

If a disease-causing mutation was identified in one of the genes listed in Appendix 1, select **Gene from Appendix 1** and add the name of the gene.

If the gene of interest cannot be found in Appendix 1, select **Other gene** and specify the name of the gene in English in accordance with the HGNC nomenclature (1). In case the exact gene is unknown, check the **Unknown** option.

Some diseases in this category may be caused by mutations in multiple genes. If that is the case, report the additionally affected gene(s) under **Mutation in additional gene**.

### *Effect of mutation*

Indicate the effect the mutation had on the molecular functions of the altered gene product.

**Gain of function** – a type of mutation that results in increased expression or activity of the altered gene product.

**Loss of function** – a type of mutation in which the altered gene product lacks the molecular function of the wild-type gene.

### *Mutation type*

Indicate the mutation type by selecting one of the options:

**Germline mutation** – a gene change in every cell in the body of the patient; germline mutations can be passed on from parents to offspring.

**Somatic mutation** – a gene change in only a subset of a body's cells. An alteration in DNA that occurs after conception. Somatic mutations can occur in any of the cells of the body except the germ cells (sperm and egg).

## Classification

Indicate the most appropriate classification of the phenotype of the IEI according to the Classification from the International Union of Immunological Societies Expert Committee (IUIS), which is updated approximately every 2 years (2).

If the **Bone marrow failures** option is selected, also complete the "Bone Marrow Failure Syndromes (BMF) incl. Aplastic Anaemia (AA)" diagnosis form in addition to the current form (optional).

## Inborn Errors of Metabolism

### Specify the gene in which a disease-causing variant was observed

If a mutation occurred in one of the genes listed in Appendix 2, select **Gene from Appendix 2** and add the name of the gene.

If the gene of interest cannot be found in Appendix 2, select **Other gene** and specify the name of the gene in English in accordance with the HGNC nomenclature (1). In case the exact gene is unknown, check the **Unknown** option.

Some diseases in this category may be caused by mutations in multiple genes. If that is the case, report the additionally affected gene(s) under **Mutation in additional gene**.

### *Effect of mutation*

Indicate the effect the mutation had on the molecular functions of the altered gene product.

**Gain of function** – a type of mutation that results in increased expression or activity of the altered gene product.

**Loss of function** – a type of mutation in which the altered gene product lacks the molecular function of the wild-type gene.

### *Mutation type*

Indicate the mutation type by selecting one of the options:

**Germline mutation** – a gene change in every cell in the body of the patient; germline mutations can be passed on from parents to offspring.

**Somatic mutation** – a gene change in only a subset of a body's cells. An alteration in DNA that occurs after conception. Somatic mutations can occur in any of the cells of the body except the germ cells (sperm and egg).

## Classification

Indicate the class and sub-class of the disease from the list of options.

**MPS** (Mucopolysaccharidosis) – a group of autosomal recessive or X-linked inherited lysosomal storage disorders affecting the metabolism of mucopolysaccharides, resulting in the accumulation of mucopolysaccharides in the body. Signs and symptoms include organomegaly, intellectual disabilities, abnormal skeletal development, heart disorders, hearing loss, and central nervous system deficiencies.

If the **MPS** class is selected, also specify the form of the disease by selecting either **Severe** or **Attenuated** (mild form).

For MPSIII and MPSIV, indicate whether the type was A or B.

**Other lysosomal storage diseases** – a group that unites lysosomal storage diseases other than MPS.

Check one of the options provided in the list; if the disease of interest is not listed, select **Other** and specify the disease name in English.

**Other metabolic disorders (non LSD)** – a group that unites all other inborn errors of metabolism that do not fall into the above-mentioned categories.

Check one of the options provided in the list; if the disease of interest is not listed, select **Other** and specify the disease name in English.

## Other Inborn Errors

### Specify the gene in which a disease-causing variant was observed

If a mutation occurred in one of the genes listed in Appendix 3, select **Gene from Appendix 3** and add the name of the gene.

If the gene of interest cannot be found in Appendix 3, select **Other gene** and specify the name of the gene in English in accordance with the HGNC nomenclature (1). In case the exact gene is unknown, check the **Unknown** option.

Some diseases in this category may be caused by mutations in multiple genes. If that is the case, report the additionally affected gene(s) under **Mutation in additional gene**.

### *Effect of mutation*

Indicate the effect the mutation had on the molecular functions of the altered gene product.

**Gain of function** – a type of mutation that results in increased expression or activity of the altered gene product.

**Loss of function** – a type of mutation in which the altered gene product lacks the molecular function of the wild-type gene.

#### *Mutation type*

Indicate the mutation type by selecting one of the options:

**Germline mutation** – a gene change in every cell in the body of the patient; germline mutations can be passed on from parents to offspring.

**Somatic mutation** – a gene change in only a subset of a body's cells. An alteration in DNA that occurs after conception. Somatic mutations can occur in any of the cells of the body except the germ cells (sperm and egg).

#### Classification

Check one of the options provided in the list; if the disease of interest is not listed, select **Other inherited platelet abnormalities** (if applicable) or, if not inherited platelet abnormality, select **Other inborn error**; and specify the disease name in English.

### *Extended dataset*

#### Immune profiling

##### Immune profiling done at diagnosis

Indicate if immune profiling was done at diagnosis.

##### Test date

Report the date of the immune profiling test. Add the date when the sample was collected for examination or (in its absence) the date indicated by a physician within the patient's medical record.

#### *Cell type and test results*

Please report the value of the cell types below from the most recent test performed. For Naive CD4 T-cells and CD8 T-cells please select the unit of measurements.

<b>Cell type</b>		<b>Unit of measurement</b>
T-cells (CD3)		Cells/ $\mu$ l
CD4 T-cells (CD4)		Cells/ $\mu$ l
CD4 T-cells (CD8)		Cells/ $\mu$ l
B-cells (CD19)		Cells/ $\mu$ l
NK-cells (CD16/CD56)		Cells/ $\mu$ l
Naive CD4 T-cells (CD4/CD45RA)		Please select the unit of measurement
Naive CD8 T-cells (CD8/CD45RA)		Please select the unit of measurement
IgG		Gram/l
IgA		Gram/l
IgM		Gram/l



## Bibliography

1. HUGO Gene Nomenclature Committee (HGNC). HUGO Gene Nomenclature Committee [Internet]. Available from: <https://www.genenames.org/>
2. Bousfiha A, Moundir A, Tangye SG, Picard C, Jeddane L, Al-Herz W, et al. The 2022 Update of IUIS Phenotypical Classification for Human Inborn Errors of Immunity. *J Clin Immunol*. 2022 Oct;42(7):1508–20.