

User Manual for the GAIN Registry as part of the ESID Registry

Version 1.1 - 15/02/2021



ESID Online Registry



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1 Introduction

Welcome in the GAIN Registry. If you are new to the ESID registry please read the [manual of the ESID registry](#), which is written really well. In this section you find some information about who we are and what are our goals. In the following sections we explain what is special to the GAIN registry, which is an optional subunit of the ESID registry.

If you have any questions regarding this manual please write to: esid-registry@uniklinik-freiburg.de

1.1. European Society for Immunodeficiencies (ESID)

“The European Society for immunodeficiencies (ESID) is a non for profit association that was created in 1994. ESID has been striving to improve the knowledge in the field of Primary Immunodeficiency (PID) by encouraging research, developing educational programs and fostering cooperation among all those involved in the diagnosis, treatment and management of these diseases.” Esid.org 2019

“The aim of the ESID registry is to build a common data pool and estimate the disease burden of primary immunodeficiencies (PID) in Europe and to provide an internet-based database for clinical and research data on patients with PID. This database is a platform for epidemiological analyses and can also serve as a tool relevant for the development of new diagnostic and therapeutic strategies or the identification of novel disease-associated genes. Several important national registries, e.g. in the UK, France, The Netherlands, Spain, Italy and Germany share their data with the ESID registry, thus providing an important backbone for this common European effort.” Esid.org 2019

1.1 German multi-organ Auto-Immunity Network (GAIN)

The German multi-organ Auto-Immunity Network (GAIN) is an association of physicians and scientists from the four universities of Freiburg, Hanover, Munich and Kiel. The consortium's objective is the research of multi-organ autoimmune diseases in eleven subprojects. One subproject (#2) is the GAIN-Registry.

The aim of the GAIN Registry is to document genetic, clinical and laboratory data as well as data on therapy and quality of life of patients with multi-organ autoimmune diseases. By means of a systematic, structured long-term recording, knowledge about the frequency and course of the diseases as well as disease-related limitations of the quality of life shall be gained. The register is intended to facilitate the identification of patients for future research projects.

1.2 Agreement for the incorporation of the GAIN registry as level 2 dataset into the ESID registry

ESID and the GAIN Consortium share the common goal to support the research of primary immunodeficiencies and immune dysregulatory diseases, in this case in particular multi-organ auto-immunities. Both parties aim to build a basis for the development of new diagnostic and therapeutic strategies and the identification of novel disease-associated genes. Therefore, both parties decided to collaborate and set-up the GAIN Registry within the ESID Registry as level 2 data set.

2 How to get a Login

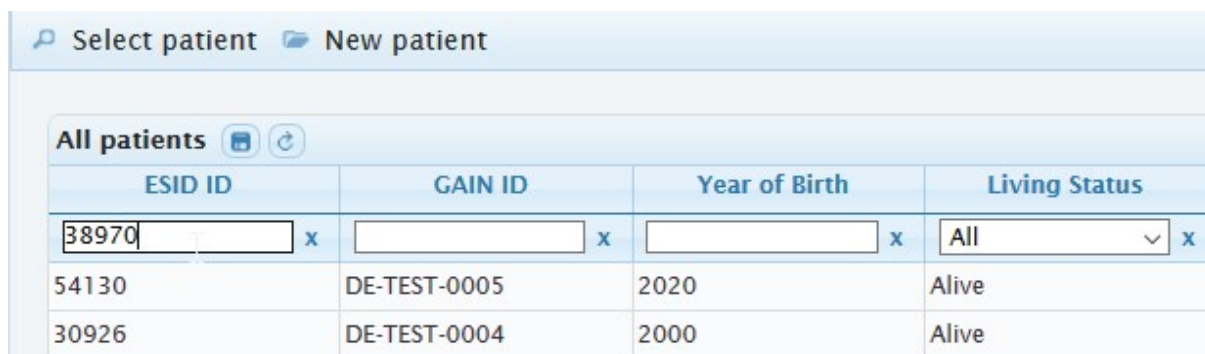
Your centre (Clinical unit) needs to be registered at the ESID registry. To register your centre and/or to apply for a login visit following [LINK](#). There you can download a form which you can send to the address specified on the documents. Please mention, when sending the application form, that your centre takes part in the GAIN Project.

3 How to register a patient for the GAIN study

There are two ways of creating a GAIN ID. Either the patient has already been registered in the ESID registry (Section 3.1), or you want to create a new patient in the registry and directly, as a short cut, include the patient to the GAIN-study and generate the GAIN-ID (Section 3.2).

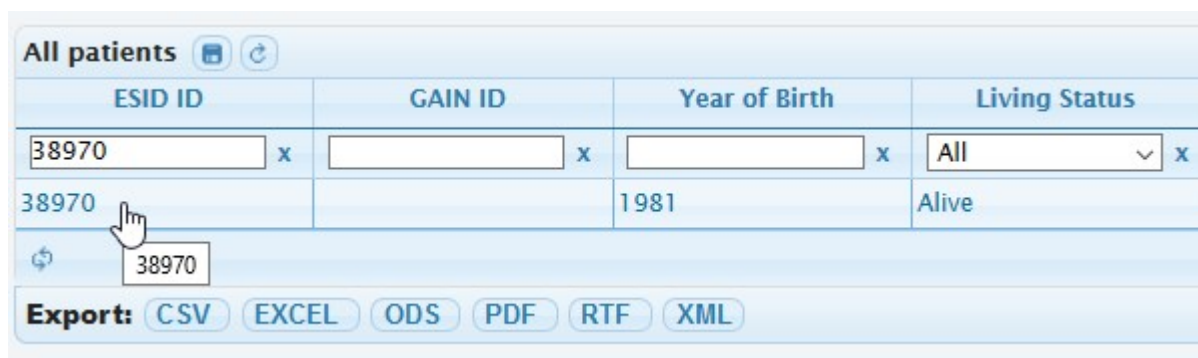
3.1 Create a GAIN ID - If the patient is already registered into ESID

1. Access the registry website <https://cci-esid-reg.uniklinik-freiburg.de/EERS/login/auth>
2. **Sign in** with your Username and Password – If you do not have a Login you can apply for one [here](#). Please mention, when sending the application form, that your centre takes part in the GAIN Project.
3. **Search for your patient** in the patient list e. g. by their ESID- ID and **open the patient form** by clicking once at the patient in the patient list.



| ESID ID | GAIN ID | Year of Birth | Living Status |
|---------|--------------|---------------|---------------|
| 38970 x | x | x | All v x |
| 54130 | DE-TEST-0005 | 2020 | Alive |
| 30926 | DE-TEST-0004 | 2000 | Alive |

Figure 1 Search a patient by his ESID ID – start searching by pressing ENTER.



| ESID ID | GAIN ID | Year of Birth | Living Status |
|---------|---------|---------------|---------------|
| 38970 x | x | x | All v x |
| 38970 | | 1981 | Alive |

Export: CSV EXCEL ODS PDF RTF XML

Figure 2 Click on the patient to open the patient form.

4. **Open the “Studies” tab.**

If the patient is already enrolled in another study press “Add New”.

If this is the first study the patient is included you can directly **select “GAIN”** in the “Name of the study” field.

Figure 3 If the patient was not included in any study before, you can directly choose “GAIN” as “Name of the study”.

Figure 4 If the patient is already enrolled in another study (here the fake example-Id sdfsdfsd) click on “Add New”.

5. Now you are asked for the **date of registration**.



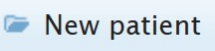

Additionally, you might receive a **notice** that you can only start documenting in the GAIN-Level2 dataset (special fields for the GAIN study) if the patient has a **GDPR (General Data Protection Regulation) conform informed consent**. A GAIN-ID will be assigned to the patient if you **click “Save”**, independent of the consent.

6. Click **“Save”**.
7. Now the Generated GAIN-ID is visible in the short patient summary at the top and in the first column of the table of the studies. **Please document this GAIN-ID into your clinic**

information system, so you know which patient belongs to this ID. If you miss this link between ID and Patient – we cannot help you.

3.2 Create a GAIN ID - If the patient was not registered in ESID before

1. Access the ESID Registry website <https://cci-esid-reg.uniklinik-freiburg.de/EERS/login/auth>
2. **Sign in** with your Username and Password – If you do not have a Login you can apply for one [here](#). Please mention, when sending the application form, that your centre takes part in the GAIN Project.

3. Click on  in the top bar of the website.
4. Now you are asked, if you want to create a patient which is part of the GAIN study – than click on .

If you just want to create a patient which is not part of the GAIN project hit



5. Now a form is shown with a reduced number of fields you need to fill in, in comparison to the number of fields when creating a normal patient. This allows a fast creation of a GAIN-ID during the normal clinic routine e. g. when you need to label a sample. Later when there is more time, someone can add more information to the patient.

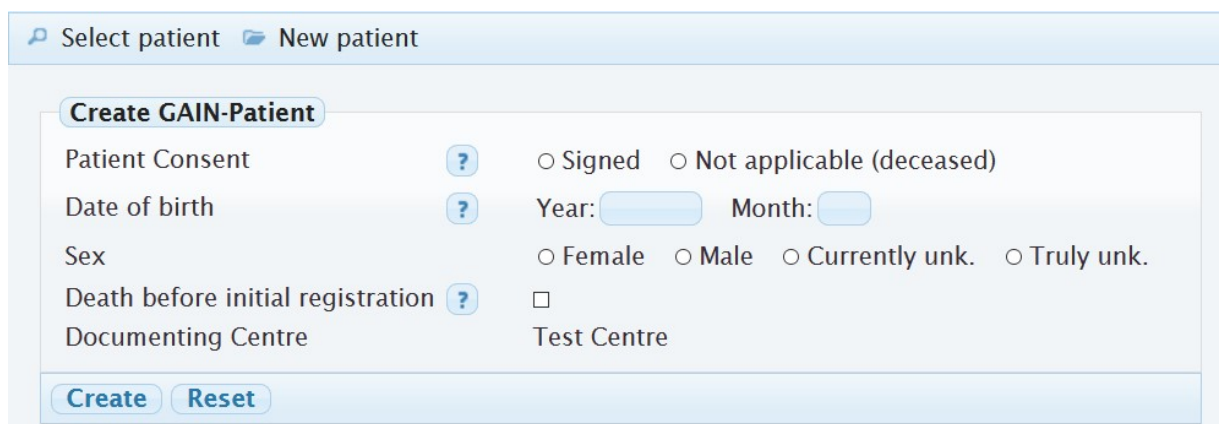


Figure 5 Fields you need to fill in for creating a GAIN patient. Other information can be added later on.

4 Understanding the GAIN-ID:

You can find the generated GAIN-ID in the short summary of the patient at the top, under the “Studies” tab in the list or in the “Patient” tab as first entry (See Figure 6 and Figure 7)

XX-XX-00-0000

The ID consists of a **country code** – a **city code** – a **number identifying each centre for multiple centres in one city** – and a **running number** for the registered patients.

E. g. for the patients from the Centrum for Chronic Immunodeficiency in Freiburg, Germany the GAIN-ID looks like the following: **DE-FR-01-0004**

ESID ID: 30928 - **GAIN-Study-ID: DE-FR-01-0004** - Diagnosis: Factor D deficiency - Year of birth: 1988 - Patient deceased /
 Doc. date: 2018-12-10 - GAIN Last news: 2018-12-10

Patient ✓ Consent ✓ **Studies** Death info ✓ Way to Diagnosis ✓ PID Diagnosis ✓ Status ✓
 Ig-Repl. ✓ HSCT ✓ Gene therapy ✓ **GAIN Study** +

Studies List - Click on a row to edit data or add a new entry: [Add New](#)

| Study patient ID | Date of registration | Name of study |
|----------------------|----------------------|---------------|
| sdfsdfsd | 2016-05-01 | APDS |
| DE-FR-01-0004 | 2020-02-07 | GAIN |

Page 1 of 1 15 View 1 - 2 of 2

Export: CSV EXCEL ODS PDF RTF XML

Figure 6 Where to find the GAIN-ID (yellow) and the new GAIN Study tab (green)

ESID ID: 30928 - **GAIN-Study-ID: DE-FR-01-0004** - Diagnosis: Factor D deficiency - Year of birth: 1988 - Patient deceased /
 Doc. date: 2018-12-10 - GAIN Last news: 2018-12-10

Patient ✓ Consent ✓ Studies Death info ✓ Way to Diagnosis ✓ PID Diagnosis ✓
 Status ✓ Ig-Repl. ✓ HSCT ✓ Gene therapy ✓ **GAIN Study** +

Edit Patient

GAIN-Study-ID **DE-FR-01-0004**

Patient Consent ? ☒ Signed ☐ Not applicable (deceased)

Date of birth ? Year: 1988 Month: 7

Country of Birth x ☒ Germany ☐ Currently unk. ☐ Truly unk.

Country of current residence ? x ☒ Netherlands ☐ Currently unk. ☐ Truly unk.

Sex ☒ Female ☐ Male ☐ Currently unk. ☐ Truly unk.

Figure 7 Where to find the GAIN-ID in the "Patient" tab

5 Prerequisites to fill in the GAIN dataset

If you registered the patient for the GAIN study there are two prerequisites before start documenting the GAIN dataset.

1. The first prerequisite is to fill in all level 1 tabs completely. You can see if a tab is not complete if a flag symbol is visible on the tab. Prerequisite is true for all level 2 datasets (studies) in the ESID registry. Now after finishing this step the GAIN tab becomes visible for the first time.
2. The second prerequisite is a GDPR conform consent. This is due to the new data protection law of the EU. A patient needs to have filled in a new GDPR conform consent which clarified his rights regarding his data. An already deceased patient does not need to have filled in a GDPR conform consent.

Now the GAIN dataset is ready to be filled in.

6 Overview of the GAIN dataset structure

The GAIN dataset is a study in the ESID registry. The ESID registry has its own Level 1 tabs e.g. “Patient” and “Way to Diagnosis”. If you followed the instructions in chapter 5 you will see the tab “GAIN Study” in addition.

6.1 Tab Hierarchy

The GAIN dataset is structured like a patient record. It has main tabs e.g. “Medical History” which are divided into sub-tabs e.g. “Surgery”, “Vaccination” and “Allergy”. The most important main tab is called “Main Questions”. Depending on the answers you set here other main- and sub-tabs open for the patient

One tab can have several forms, which need to be saved separately. One example is the sub-tab of “Diagnostics” called “Neurological Diagnostic”. There you can find the forms “Cerebrospinal fluid analysis” and “Nano Scale”.

| Name | Date of Sample | Value | calculated | Marker combination | Value not available |
|--------------------------|----------------|---------|------------|--------------------|--------------------------|
| Lymphocytes | | = /μL | | | <input type="checkbox"/> |
| CD19+ cells | | = /μL % | | | <input type="checkbox"/> |
| „Transitional“ B-cells | | = /μL % | | IgM+ CD38++ | <input type="checkbox"/> |
| „MZ like memory“ B-cells | | = /μL % | | CD27+ IgD+ | <input type="checkbox"/> |
| „Memory“ B-cells | | = /μL % | | IgD- CD27+ | <input type="checkbox"/> |
| CD21 low B-cells | | = /μL % | | CD21 low | <input type="checkbox"/> |

Figure 8 Example of tab hierarchy in GAIN

6.2 Time-structure or where are my previously entered data

Normally, a patient is documented once, when he first enters the GAIN registry. This is the most laborious and takes most of the time. This step is called “baseline”. The patient’s information should be updated each time the patient comes to the clinic. Most importantly each time the patient donates a bio sample (blood etc.) for research, as we need e.g. the information of the medication on the date of the sample. At least each time a year we need any information about the patient, even if the patient did not went to the clinic anymore. A phone call is sometimes enough. These “up dates” from the patients are called “Follow-ups”. The date of the “study visit” is the date we collected the information. E. g. the date when the patient went to the clinic to see the clinician/ to donate a sample or the patient was called via phone.

Some tabs are saved connected directly to the patient. These tabs can be adapted over time but only exist once. Other tabs are connected to the study visit date. Each study visit they can be filled out again and can therefore exist multiple times.

Tabs connected to the patient (exist once):

- Main questions

- ESID level 1 complement
- Medical History
- Diagnosis
- Therapy

Tabs connected to the study visit date (exist multiple times - once per study visit):

- Diagnostics
- Questionnaires

If you are searching for the entries you did in a previous study visit in a tab which exists multiple times you need to open the respective follow-up. You can find this in the short description line of the patient next to “Doc. date”. Make sure that you switch back to the study visit date your information belongs to before start documenting again.



Figure 9 How to change to a previous follow-up documentation

7 Mandatory or preselected tabs

Some tabs are preselected to be filled out. They exist for the patient regardless of the answers in the “Main Questions” tab.

- ESID level 1 complement
 - Demographic Data
 - Death complement
- Diagnosis
 - Main Diagnosis
- Diagnostics
 - Central Diagnostics
 - Physical Examination
- Questionnaires

8 User interface

8.1 Forms folding into tables

Some tabs look when you fill them the first time like an ordinary form you can only fill in once. But when completed they fold into one row of a table. At the top of the table you will find an “Add” button and you can fill in the form again which will result in a next row of the table.

The left screenshot shows the 'Create Vaccination' form. It has tabs for 'Surgery' and 'Vaccination'. Under 'Vaccination', there are sections for 'Kind of Vaccination', 'Specific Herpes Zoster vaccine', 'Specific Streptococcus pneumoniae vaccine', 'Was the vaccination titre measured?', 'Date of titre measurement', and 'Vaccination titre'. The right screenshot shows the 'Vaccination List' table. It has a header row with columns: 'Kind of vaccination', 'Date of Vaccination', 'Specific Streptococcus p', 'Specific Herpes Zoster v', 'Was the vaccination titre', 'Date of titre measure', and 'Vaccination titre'. Below the header is a table with one row: 'Influenza (Grippe)', '2021-02-01', and 'No'. There is an 'Add New' button and an 'Export' section with options: CSV, EXCEL, ODS, PDF, RTF, XML.

Figure 10 Example for a form which “folds” into a table after it has been filled out. With the “Add New” button you can open a new form to document the next vaccination.

If you change the content of one row you overwrite its content. We don’t know what was standing there before. Therefore, if you need to make changes over time, enter a new row containing the changed content. E.g. when the doses or frequency for the medications changes you need to enter the medication with changed doses/frequency as new row again. Don’t forget to adapt the start and end dates.

Some special tables have additional tables in each form. One example is the medication form. You can enter several side effects for one medication. So in the form for the medication you can open a form for the side effect. When filled out the side effects will result in a table. And when the medication form is filled out completely it will fold into a table as well.

The top left screenshot shows the 'Create Medication' form. It has tabs for 'Surgery' and 'Medication'. Under 'Medication', there are sections for 'Indication - Link to disease or symptom', 'ATC Code', 'ATC Agent', 'Drug Name', 'Route of administration', 'Kind of treatment', 'Dosage per administration', 'Frequency of medication (level 1)', 'Frequency of medication (level 2)', 'Irregular', 'Start date', 'End date', 'Compliance', and 'Benefit'. The top right screenshot shows the 'Create Adverse drug event' form. It has a section for 'Create Adverse drug event' with fields for 'Description', 'Start date', 'End date', 'Compliance', and 'Benefit'. The bottom left screenshot shows the 'Medication List' table. It has a header row with columns: 'Indication', 'ATC Code', 'ATC Agent', 'Drug Name', 'Route of administration', 'Kind of treatment', 'Dosage per administration', 'Frequency of medication (level 1)', 'Frequency of medication (level 2)', 'Irregular', 'Start date', 'End date', 'Compliance', 'Benefit', and 'Adverse'. Below the header is a table with one row: 'Diabetes', 'A10BD17', 'Metformin and acarbose', 'Metformin', 'oral', 'only treatment', '3', 'times(s) per day', 'every 1', 'day', '2021-01-03', '2021-02-01', 'No', 'Yes', 'Yes'. The bottom right screenshot shows the 'Edit Medication' form. It has a section for 'Edit Medication' with fields for 'Drug Name', 'Route of administration', 'Kind of treatment', 'Dosage per administration', 'Frequency of medication (level 1)', 'Frequency of medication (level 2)', 'Irregular', 'Start date', 'End date', 'Compliance', and 'Benefit'. At the bottom, there is an 'Adverse drug event List' table with columns: 'Description', 'Certainty', 'Start date', 'Start date unknown', 'End date', and 'End date unknown'. Below the header is a table with one row: 'diarrhea', 'certain', '2021-01-29', and 'Currently unk.'.

Figure 11 When you have filled in a medication you can add an adverse drug event by selecting “Add first Adverse drug event Entry”. The small form for adverse drug event opens. After saving you see the entire list of medications again (here only one entry). When you open that entry you see that there is now a table for adverse drug events. You can add multiple adverse drug events for one medication entry.


9 Description of tabs

9.1 Main questions tab

Tab connected to the patient (exist once)

The main questions tab is the most important one, as it controls which other tabs and sub-tabs can be filled out for the patient (See Figure 11 and Figure 12). It needs to be updated for the patient in each study visit. E.g. The “Medical History” and the Subtab “Surgery” becomes visible for the patient when you answer the question “Has the patient ever experienced a surgery?” with “yes”. When you change your answer from “yes” to “no” you will be warned: Any information entered into the tab, you are removing by answering “no”, will be deleted.

In addition the “Date of GAIN study visit” will be entered in this tab. This value is extremely important, as all tabs which can be filled out several times will be saved connected to this date. E.g. the questionnaires can be filled out every study visit. And each filled out questionnaire will be saved connected to the study visit date entered at the “main questions” tab.

Information hidden behind the question mark symbols  is especially useful to discriminate acute and persistent infections.

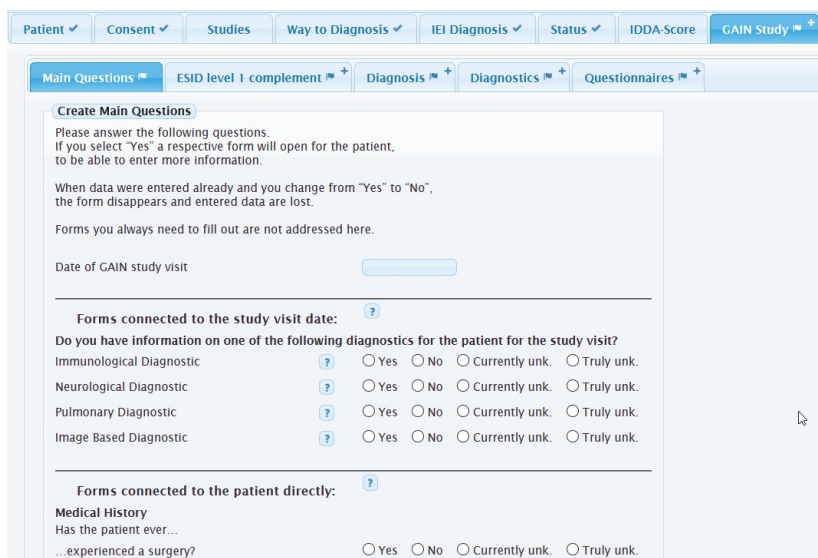


Figure 12 The tab “Medical History” is not available yet when the “Main Questions” tab was not filled out.

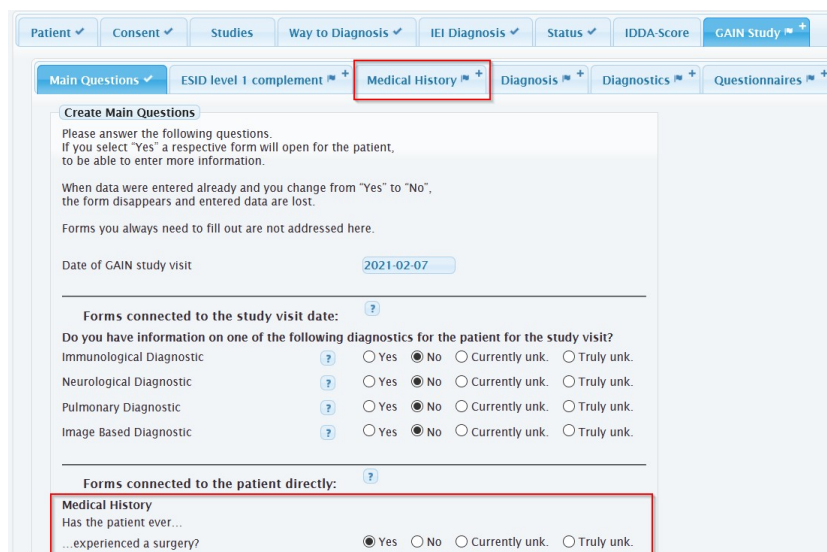


Figure 13 you answer one question belonging to the Medical History category with “yes” (lower red box) and save the “Main Questions” form you see (first red box) that this tab is available now.

9.2 ESID level 1 complement

Tab connected to the patient (exist once)

The ESID Level 1 dataset already includes information interesting for the GAIN consortium but it is in some aspects not detailed enough. Therefore, we included an ESID complement tab which adds some aspects to the basic ESID level 1 dataset.

9.3 Medical History

Tab connected to the patient (exist once)

9.4 Diagnosis

Tab connected to the patient (exist once)

9.4.1 Main diagnosis

Here you will fill in the main diagnosis of the patient. It is similar to the level 1 IEI diagnosis, only that you should code the diagnosis in ICD-11, which is much more detailed, than the previous ICD-10 code system. It is now possible to differentiate between different types of “CVID Common Variable Immunodeficiencies”.

9.4.2 Concomitant diagnosis

Please document here diseases which are not related to or result from the inborn error of immunity. Only document diseases which reduce the health of a patient permanently or when the patient needs to take medication because of this disease. Examples are polyneuropathy, hypertension, amenorrhea and breast cancer.

9.4.3 Genetic diagnosis

This tab is very complex for people not common with genetic term. Therefore, there is a lot of descriptive text hidden behind the question marks. Nevertheless, it is a very important tab, as it is the basis for further genotype- phenotype correlations the registry is aiming at. So please make yourself familiar with it and help us collecting this important information. Feel free to contact us, when having troubles with it.

The “get transcripts” button works as the following: You can enter a name of gene the patient has a mutation in and hit the button “get transcripts”. Only then one of the matching transcripts can be selected.

The screenshot displays a web interface for searching transcripts. On the left, there is a list of search criteria with question marks: 'Search transcripts by gene', 'Transcript (ensembl nomenclature)', 'Transcript (RefSeq nomenclature)', 'Variant on allele 1 p.', 'Variant on allele 1 c.', 'Variant on allele 2 p.', and 'Variant on allele 2 c.'. In the center, a text input field contains 'ctla4'. To its right is a button labeled 'get transcripts'. Below the input field, a dropdown menu is open, showing a list of transcripts: 'ENST00000295854.10 (CTLA4)', 'ENST00000302823.8 (CTLA4)', 'ENST00000472206.1 (CTLA4)', 'ENST00000487393.1 (CTLA4)', and 'ENST00000648405.2 (CTLA4)'. At the bottom left of the interface are 'Save' and 'Reset' buttons.

As you have all chromosomes twice, one from your father and one of your mother, you have for each gene two so called “alleles”. It is possible you inherited this mutation only from one of your parents, so only one allele is affected. Than the other allele works as normal and has a “wild type” state. But if both of your parents passed the mutation on to you, both alleles are affected and you should also document which variant has the second allele.

9.4.4 Organ related involvement

The most versatile sub tab is the organ related involvement tab. You can enter here everything the patient suffers from except malignancies and infections, which are covered by other sub-tabs.

A lot of diseases (ICD-11 coded) can be entered here.

9.5 Diagnostics

Tab connected to the study visit date (exist multiple times - once per study visit)

9.6 Therapy

Tab connected to the patient (exist once)

9.7 Questionnaires

Tab connected to the study visit date (exist multiple times - once per study visit)

The questionnaires should be filled out as the patient did. This includes also several answers, if the patient could not decide for one option.

How did the patient/the parents assess the patient's current health-related quality of life? ☒very good ☒good ☐moderate ☐bad ☐very bad ☐do not know

If the patient did not fill in a question choose "Truly unk."

If the patient crossed several answers, which are not coherent (e. g. Yes AND No), choose "Truly unk."

Some answers of the printed questionnaire you will not find in this tab, but they belong to other tabs in the registry e.g. Level 1 questions or the weight and height of the patient.

Feel free to add handwritten notes into the "remarks" field.

10 FAQ

- *I cannot select the GAIN study in the studies list.*

It might be that your centre is currently not registered as part of GAIN. Please contact the [ESID-Registry Support](#).

- *I cannot add a GAIN follow up.*

You can only add a GAIN follow up if all actual GAIN forms and the level 1 dataset are marked as complete (no flags anymore) and the current date lies after the current date of documentation.

- *I don't find the data I filled in when I documented the last time.*

Check chapter 6.2. Your data might be entered in a different follow-up. Some tabs can be entered per follow-up and are not visible in the next one.

- *I cannot find the gene in the genetic diagnosis tab I am looking for.*

Please check first if there is a synonym for the gene and try those. E.g. the TACI gene is also called TNFRSF13B. You can find a good overview in <https://www.genecards.org/> If you are still missing an option please send us an E-mail to the [ESID-Registry Support](#).

- *Is the diagnosis date of the main diagnosis for level 1 and level 2 always the same?*

No it is not. In level 1 the first IEI diagnosis ever diagnosed for the patient is asked. In the GAIN level 2 dataset you are asked to document the diagnosis date for this specific diagnosis in particular.