



# **Guide to Phenome Analyzer 2019**

***AI-based, human-curated  
Diagnostic Decision Support Software***

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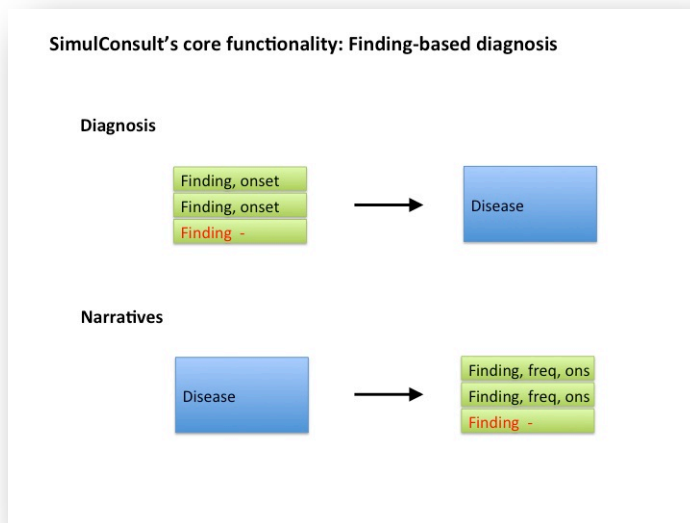
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# WELCOME!

Narrative medical resources enable medical professionals to start with a disease and learn about its findings (symptoms, signs and tests). Patients, of course, appear the other way: with findings that medical professionals need to use to deduce the diagnosis from thousands of known disease phenotypes. The group of all such disease phenotypes is called the “Phenome”. SimulConsult has been built to help solve this diagnostic problem, enabling clinicians to start with findings and get to the correct diagnosis. In doing so, it offers a “differential diagnosis” consisting of a list of likely diseases with some indication of their relative probability.

Figure 1: SimulConsult's core functionality: finding-based Diagnosis



**SimulConsult 2.0** comprises a proprietary computational database of diseases and their characteristics, patented AI-based algorithms and intuitive, easy to use user interface.

- **Database.** Specialists curate and update the database continuously with information from the peer-reviewed literature and relevant unpublished disease characteristics. The company has a well-established, efficient approach to data-gathering. Each year, the database grows by 500-1,000 diseases.
- **Patented algorithms.** The company has received 4 issued U.S. patents (6,212,519; 6,754,655; 7,742,932 & 9,524,373)
- **User interface.** The user interface **simplifies input** of onset (or absence) of patient symptoms and physician-observed signs and test results (“findings”); **computes and displays** likelihood-weighted potential diagnoses (“differential diagnosis”) that evolves as data is entered; **suggests** the most useful clinical findings and tests, which are most likely to shorten the list of diagnoses; and **connects** instantly to precise narrative resources about the disease or finding under consideration. The results improve accuracy, lower costs and increase physician productivity.

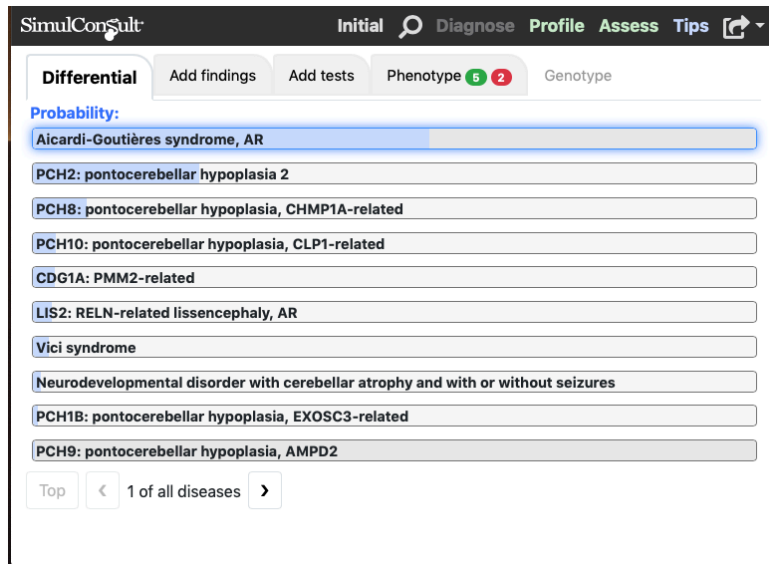
A Genome-Phenome Module that enables interpretation of genomic results in the clinical context is an optional upgrade.

# INTRODUCTION TO A FEW SIMULCONSULT CONVENTIONS

## Colors and their meaning

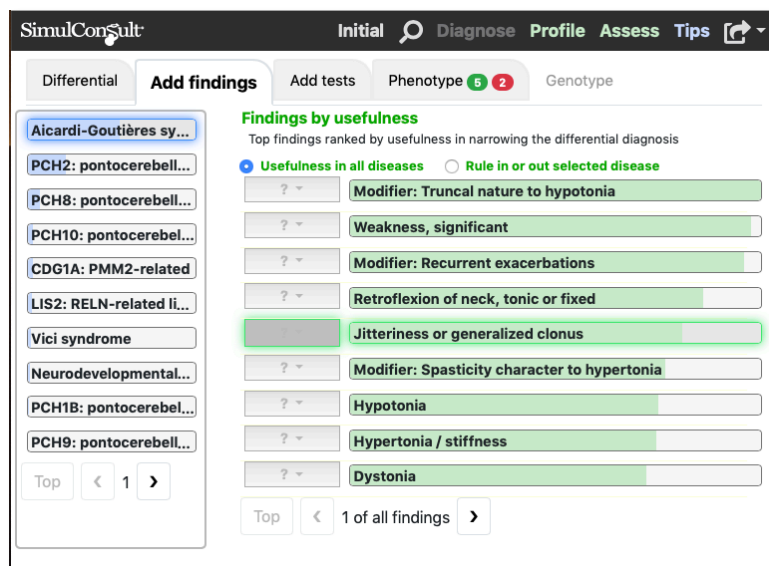
Diseases are **blue**. Findings are **green**.

Figure 2: The Differential Diagnosis with likelihood shown in blue



The main diagnostic screen shows a miniaturized differential diagnosis, together with other useful information. In this case, the software shows suggested useful clinical findings.

Figure 3: Suggested findings ranked in order of Usefulness in Narrowing the Differential Diagnosis



## PATIENT CASE USED FOR ILLUSTRATIONS

This Very Low Density Lipoprotein Receptor (VLDLR) case was published by Dixon and Salazar in 2012 and will be used throughout for illustrating the points.

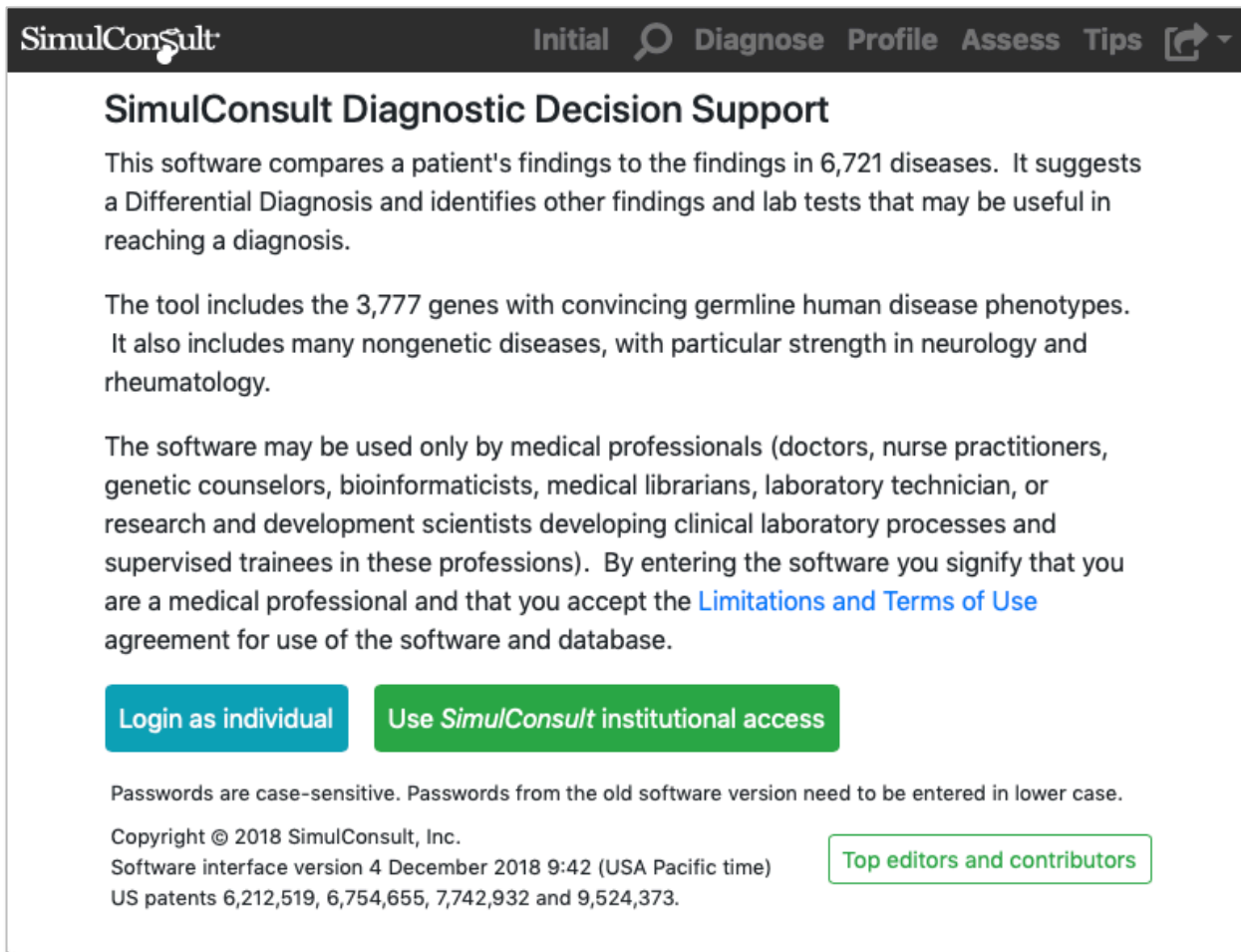
### A 2-year old boy from the Middle East

- **Family history:**
  - Neither parent affected
  - 1 of 2 brothers affected
  - Parent consanguinity: first cousins
- **At 1 month:** microcephaly
- **By 1 month:** Nystagmus, non-rotary
- **By 6 months:** hyperreflexia
- **Absent:** regression
- **MRI:** pan cerebellar hypoplasia

## GET STARTED

On the login page you can see the number of diseases and genes covered. The editors and contributors can also be seen using the link from this page.

Figure 4: Login



The screenshot shows the SimulConsult website interface. At the top, there is a navigation bar with the SimulConsult logo on the left and menu items: Initial, Diagnose, Profile, Assess, and Tips. Below the navigation bar, the main heading is "SimulConsult Diagnostic Decision Support". The page contains three paragraphs of text describing the software's capabilities and user requirements. There are two prominent buttons: "Login as individual" (blue) and "Use SimulConsult institutional access" (green). At the bottom, there is a "Top editors and contributors" link in a green box, along with copyright and patent information.

Initial Diagnose Profile Assess Tips

### SimulConsult Diagnostic Decision Support

This software compares a patient's findings to the findings in 6,721 diseases. It suggests a Differential Diagnosis and identifies other findings and lab tests that may be useful in reaching a diagnosis.

The tool includes the 3,777 genes with convincing germline human disease phenotypes. It also includes many nongenetic diseases, with particular strength in neurology and rheumatology.

The software may be used only by medical professionals (doctors, nurse practitioners, genetic counselors, bioinformaticists, medical librarians, laboratory technician, or research and development scientists developing clinical laboratory processes and supervised trainees in these professions). By entering the software you signify that you are a medical professional and that you accept the [Limitations and Terms of Use](#) agreement for use of the software and database.

[Login as individual](#) [Use SimulConsult institutional access](#)

Passwords are case-sensitive. Passwords from the old software version need to be entered in lower case.

Copyright © 2018 SimulConsult, Inc.  
Software interface version 4 December 2018 9:42 (USA Pacific time)  
US patents 6,212,519, 6,754,655, 7,742,932 and 9,524,373.

[Top editors and contributors](#)

Note that on the above page we publish the number of genes and diseases currently in the database.

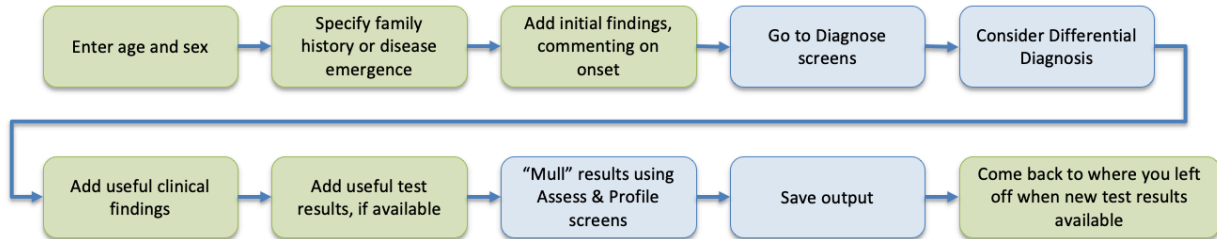
### **Enterprise version (Health system or Laboratory): Access from within EHR or LIM.**

*If you have the electronic health record or laboratory information system integrated version, please see the companion document for how to launch SimulConsult from within your system.*

## Basic process

Diagnosis is usually an iterative task. SimulConsult 2.0 emulates the doctor's iterative decision making process, especially for more complex cases.

Figure 5: Process flow for diagnosis using SimulConsult



## Start a new patient, by entering age and sex

Once the age and sex are entered, you have multiple options for entering findings. Note that in the Enterprise version integrated with the electronic health record (EHR), age and sex are automatically imported.

Figure 6: Initial screen, where you specify the age, units and sex

SimulConsult Initial Diagnose Profile Assess Tips

### Initial information about the patient

Start a new patient

**Age\*** Age now  Days  Weeks  Months  Years

**Sex\***  Male  Female (Use presumed chromosomal sex)

*Optional:*

**Care setting**  Primary  Secondary  Tertiary

**Emergence** (Emergence of most recent episode of clinical findings)

**Family history**

**Exposure history**

**Died**

**Onset considered**

When adding findings, begin with the ones that are most clearly present and unusual. Pertinent negatives are as important as pertinent positives, and onsets can be crucial.

Next: Add a finding using

## Enter Family history

You can enter family history if you know it by checking family history. While the family history shown here will obviously increase the probability of the diagnosis being a recessive disease, non-genetic diseases continue to be considered.

Figure 7: Entering family history

SimulConsult Initial Diagnose Profile Assess Tips

### Initial information about the patient Start a new patient

Age   Days  Weeks  Months  Years

Sex  Male  Female (Use presumed chromosomal sex)

*Optional:*

Care setting  Primary  Secondary  Tertiary (Tertiary ignores disease incidence)

**Emergency** (Emergence of most recent episode of clinical findings)

**Family history**

Mother affected:  Unknown  No  Yes

Father affected:  Unknown  No  Yes

Sisters affected:  of  by similar age

Brothers affected:  of  by similar age

Maternal uncles affected:  of  total

Parental consanguinity:

**Exposure history**

**Died**

**Onset considered**

When adding findings, begin with the ones that are most clearly present and unusual. Pertinent negatives are as important as pertinent positives, and onsets can be crucial.

**Next: Add a finding using**



## ENTER INITIAL KEY FINDINGS

The process of entering clinical findings (signs, symptoms) and test results has been optimized for speed, including prompting the clinician to comment on findings most helpful in narrowing the evolving differential diagnosis (the probability weighted list of potential diagnoses relevant for this patient based on findings entered).

### Modes for entering findings

You have several search modes for locating **the initial** findings, each of which is illustrated below.

1. **Core finding lists** (common findings in genetics, neurology, rheumatology and ancestry, as well as an interface for family history)
2. **Search** for findings (one or more terms)
3. **Disease profile** is useful if you have a strong hypothesis. Once 3-5 findings are entered, move to the general diagnose screen to get the benefit of suggestions based on the evolving differential diagnosis.
4. **Useful findings** and **Useful tests** tabs will often be the most convenient way to add findings once the user has gotten an initial differential diagnosis.

## Enter using “Core finding lists”

Using the “Neurology Core finding lists” you can add a set of pertinent positives and negatives.

Core finding lists are developed as a set of up to 46 findings most often used in the referrals to the specialty. Core finding lists allow the user to increase the speed with which the software focuses on the relevant subset of diseases. To ensure the Core Finding List is most useful, the curation process for new and updated disease reviews the findings in the Core Finding List to ensure complete coverage.

With the addition of new specialties, new Core Finding Lists are added

Figure 8: Entering findings using the Neurology Core finding lists

SimulConsult Initial Diagnose Profile Assess Tips

### Core finding lists for specialties

None  Exercise, fatigue  Metabolic  Mitochondrial  
 Neurology  Rheum clinical  Rheum tests  
 Size & Vitals

? -	Ataxia
? -	Attention deficit
? -	Autistic behavior
? -	Choreoathetosis
? -	Contractures or limited range of motion
? -	Cramps, frequent or severe
? -	Creatine kinase high
? -	Dysarthria or abnormal sound character
? -	Dysphagia or feeding difficulty
? -	Dystonia
? -	Eye movement deficit, horizontal
? -	Gait abnormality
? -	Headache (frequent or severe)
? -	Hearing impairment
* -	≤6m
? -	Hyperreflexia
? -	Hypertonia / stiffness
? -	Hypoaesthesia
? -	Hyporeflexia
? -	Hypotonia
? -	Intellectual disability
? -	Irritability or agitation, pronounced
? -	Modifier: Location distal: motor /joint
? -	Modifier: Location: proximal motor or s...
? -	Modifier: Recurrent exacerbations
? -	Modifier: Unilateral location or asymme...
? -	Motor developmental delay
Bundle -	MRI scan of the brain
? -	Muscular atrophy or hypoplasia
? -	Myoclonus
* -	≤1m
? -	Nystagmus, non-rotary
? -	Optic atrophy or hypoplasia
? -	Protein high in CSF
X -	Regression
? -	Scoliosis with or without kyphosis
? -	Seizures with abnormal movements
? -	Sleep disturbance

## Enter findings using search

As the user types into the search box, all the findings appear as buttons below. The search considers both the finding name and the synonyms known for that finding. SimulConsult supports many synonyms. You can put more than one search term in the box at a time, separate them with a space. Often it is best to use a word fragment if different endings are used, such as “nyst” for nystagmus.

Figure 9: Entering findings via search

The screenshot shows the SimulConsult interface. At the top, there is a navigation bar with the SimulConsult logo and buttons for 'Initial', 'Diagnose', 'Profile', 'Assess', and 'Tips'. The 'Diagnose' button is highlighted. Below the navigation bar, the page is titled 'Core finding lists for specialties' with several radio button options: 'None' (selected), 'Exercise, fatigue', 'Metabolic', 'Mitochondrial', 'Neurology', 'Rheum clinical', 'Rheum tests', and 'Size & Vitals'. Underneath, there is a section 'Search for a finding' with a search input field containing 'nysta' and a clear button 'X'. Below the search field, there is a text box explaining: 'Use the box immediately to the left of findings to specify presence (or absence). A second box allows specifying required findings.' This is followed by three rows of search results, each with a dropdown menu on the left and a text box on the right. The first row shows a dropdown with '?' and a text box containing 'Nystagmus, rotary'. The second row shows a dropdown with '≤1m' and a text box containing 'Nystagmus, non-rotary'. The third row shows a dropdown with '?' and a text box containing 'FRMD7 gene variant (X-linked)'. Below this, there is a section 'Search for a disease' with a search input field containing 'Find diseases that have all these terms' and a clear button 'X'. At the bottom, there is a text box with instructions: 'The **Diagnose** screen is the core of the software. Use its capabilities or to keep adding findings until you are satisfied with the diagnosis or workup. The top navigation bar has other screens, including for outputs and re-loading a previous patient.' Below this text box is a dark button with the text 'Next: Explore the differential diagnosis using **Diagnose**'.

## Enter findings using a disease where there is a strong hypothesis

If the user has a strong hypothesis of the diagnosis, they can begin by typing the disease name into the blue disease search box. Matching diseases appear as buttons below. Then by clicking on the disease button and the profile option, the user can begin by entering findings associated with that disease. It is best not to add more than 3-5 pertinent positives before going to the general diagnose screen, so as not to over specify the answer.

Figure 10: Entering findings via the disease profile

**SimulConsult** Initial Diagnose Profile Assess Tips

### Core finding lists for specialties

None 
  Exercise, fatigue 
  Metabolic 
  Mitochondrial 
  Neurology 
  Rheum clinical 
  Rheum tests 
  Size & Vitals

### Search for a finding

Find symptoms, signs and tests that have all these terms X

### Search for a disease

pch2

**PCH2: pontocerebellar hypoplasia 2**

The **Diagnose** screen is the core of the software satisfied with the diagnosis or workup.  
The top navigation bar has other screens, including **Diagnose**.

**Next: Explore the differential diagnosis**

#### Profile disease: PCH2: pontocerebellar hypoplasia 2

Younger Older

Require	Presence	Findings in this disease	Frequency @3 yo	Gone	Later
<input type="checkbox"/>	? -	Intellectual disability			
<input type="checkbox"/>	? -	CT or MRI: pontine atrophy or hypoplasia			
<input checked="" type="checkbox"/>	@1m	Microcephaly			
<input type="checkbox"/>	? -	Motor developmental delay			
<input type="checkbox"/>	? -	Dystonia			
<input type="checkbox"/>	? -	Choreoathetosis			
<input checked="" type="checkbox"/>	✓ -	CT or MRI: pan-cerebellar atrophy or hypoplasia			
<input type="checkbox"/>	? -	CT or MRI: brainstem atrophy or hypoplasia			
<input type="checkbox"/>	? -	TSEN54 gene variants (biallelic)			
<input type="checkbox"/>	? -	Jitteriness or generalized clonus			
<input type="checkbox"/>	? -	CT or MRI: cerebral cortex atrophy or hypoplasia			
<input type="checkbox"/>	? -	Gait abnormality			
<input type="checkbox"/>	? -	Seizures with abnormal movements			
<input type="checkbox"/>	? -	Myoclonus			
<input checked="" type="checkbox"/>	≤6m	Hyperreflexia			
<input type="checkbox"/>	? -	Retroflexion of neck, tonic or fixed			
<input checked="" type="checkbox"/>	X -	Early death if undiagnosed			
<input type="checkbox"/>	? -	Sleep apnea			
<input type="checkbox"/>	? -	Dysphagia or feeding difficulty			
<input type="checkbox"/>	? -	Hypertonia / stiffness			

Top < 1 of 3 >

## The importance of onset information

Most genetic diseases unfold over time, and as a result, using information available about the **onset of particular findings** is helpful in narrowing the differential diagnosis. Clicking on the box next to the finding brings up a dialog box of onset options. After you specify the onset the box automatically closes and a short-hand appears in the box next to finding. To enter a finding, click to the left of the finding where you see the “**? and the down arrow.**” The menu will appear. Click on the selection you want.

### 1. Pertinent positive options

- a. Onset **at** a particular age
- b. Present **by** a particular age, onset unknown (not as informative as option “a” but sometimes all that is known)
- c. Present, onset unknown

### 2. Pertinent negative option

- a. Absent now

Figure 11: Specifying Onset

The screenshot shows the SimulConsult interface. At the top, there is a navigation bar with 'Initial', 'Diagnose', 'Profile', 'Assess', and 'Tips'. Below this, there are radio buttons for 'Core finding lists for specialties' including 'None', 'Exercise, fatigue', 'Metabolic', 'Mitochondrial', 'Neurology', 'Rheum clinical', 'Rheum tests', and 'Size & Vitals'. A search box contains 'nysta'. Below the search box, there is a list of findings: 'Nystagmus, rotary', 'Nystagmus, non-rotary', and another finding. A dropdown menu is open for 'Nystagmus, non-rotary', showing options: 'Present, recent onset (≥2 years)', 'Present, known onset earlier', 'Present, noticed earlier', 'Present, unknown onset', 'Absent', and 'Not specified'. A button with '≤1m' is highlighted. At the bottom, there is a 'Next: Explore the differential diagnosis using Diagnose' button.

## The importance of emergence

For other diseases, such as those in rheumatology, the **speed of emergence** is key. This is done at the macro level for all findings on the Initial screen.

Figure 12: Commenting on the speed of Emergence

SimulConsult Initial Diagnose Profile Assess Tips

### Initial information about the patient

[Start a new patient](#)

Age   Days  Weeks  Months  Years

Sex  Male  Female (Use presumed chromosomal sex)

*Optional:*

Care setting  Primary  Secondary  Tertiary (Tertiary ignores disease incidence)

**Emergence\***   Minutes  Hours  Days  Weeks  Months  Years

(Emergence of most recent episode of clinical findings)

Family history

Exposure history

Died

Onset considered

When adding findings, begin with the ones that are most clearly present and unusual.  
Pertinent negatives are as important as pertinent positives, and onsets can be crucial.

**Next: Add a finding using**

## The importance of pertinent negatives

Because many genetic diseases share multiple findings, geneticists usually make heavy use of the absence of pertinent findings during the process of diagnosis. The software also supports this option.

Figure 13: Noting a pertinent negative

The screenshot shows the SimulConsult interface. On the left, a list of differential diagnoses is shown, with 'CDG1A: PMM2-related' highlighted in light blue. The top navigation bar includes 'Initial', 'Diagnose', 'Profile', 'Assess', and 'Tips'. Below the navigation bar, there are tabs for 'Differential', 'Add findings', 'Add tests', 'Phenotype' (with a '2' in a green circle and a '0' in a red circle), and 'Genotype'. The main content area is titled 'Findings by usefulness' and lists various findings with progress bars. A dropdown menu is open for the 'Regression' finding, showing options: 'Present, recent onset (≥2 years)', 'Present, known onset earlier', 'Present, noticed earlier', 'Present, unknown onset', 'Absent', and 'Not specified'. A yellow callout box at the bottom left contains the text: 'TIP Notice the light blue shading representing the differential diagnosis overlay on the diseases.'

## The importance of requiring certain findings

The default in the software is to consider the possibility that a finding is not related to the primary diagnosis; the software has extensive probability information to make these assessments. However, when a common finding is particularly notable, such as a very high creatine kinase level, you have the ability to specify that you require it to be a finding in the diagnosis.

Similarly, one or more findings may be so striking or unusual that you only want to see diseases with that finding. You can require the finding, by selecting the box next to the onset box and selecting Required, which displays a "\*" to the left of the onset, as is shown below for nystagmus.

Figure 14: Requiring a finding

The screenshot shows the SimulConsult software interface. At the top, there are navigation tabs: Initial, Diagnose, Profile, Assess, and Tips. Below this, there are sub-tabs: Differential, Add findings, Add tests, Phenotype (with a '2' in a green circle and a '1' in a red circle), and Genotype. The main content area is titled '2 year old boy' and 'Pertinent positive findings'. A list of findings is shown, with 'Nystagmus, non-rotary' highlighted in green. A dropdown menu is open over this finding, showing options for severity scores (5, 4, 3, 2) and a 'Required' option (black text with an asterisk) and a 'Not required' option (grayed text with an asterisk). The 'Required' option is selected, and an asterisk is visible to the left of the finding's onset box.



## Entering tests results for tests that have multiple findings

In order to distinguish the test results from a particular laboratory or diagnostic testing panel from the general category of results, we call such collections “Bundles”. Shown here is the bundle of test results that can come back from an MRI of the brain.

Figure 15: Entering test results for tests with multiple potential findings “Bundles”

The screenshot displays the SimulConsult interface, specifically the 'Add tests' section. The top navigation bar includes 'Initial', 'Diagnose', 'Profile', 'Assess', and 'Tips'. Below this, there are tabs for 'Differential', 'Add findings', 'Add tests', 'Phenotype' (with a count of 4 and 1), and 'Genotype'. The 'Add tests' section is active, showing a list of tests ranked by usefulness. The selected test is 'MRI scan of the brain'. Below this, a list of findings is displayed, each with a dropdown arrow and a text box for input. The findings include:

- CT or MRI: pontine atrophy or hypoplasia
- CT or MRI: cerebral cortex atrophy or hypoplasia
- CT or MRI: brainstem atrophy or hypoplasia
- MRI: white matter abnormality
- CT or MRI: corpus callosum hypogenesis
- CT, MRI or head USG: hydrocephalus, not ex-vacuo
- Modifier: MRI: corpus callosum nature to white matter ...
- CT or MRI: lissencephaly
- Modifier: MRI: hypomyelination type of white matter ab...
- Modifier: MRI: periventricular predominance to brain i...
- Modifier: MRI: temporal predominance to brain imaging...
- CT or MRI: vermal cerebellar atrophy or hypoplasia
- CT or MRI: brain cysts or cavities
- Modifier: MRI: posterior fossa predominance to brain i...
- CT or MRI: 4th ventricle enlargement, major
- Modifier: MRI: frontal predominance to brain imaging a...
- CT or MRI: thick cortex
- CT or MRI: basal ganglia abnormalities
- MRI: polymicrogyria
- Modifier: MRI: multifocal distribution to white matter...

The interface also includes a search bar, a 'Bundle' dropdown menu, and a 'All tests' button. The 'Usefulness in all diseases' radio button is selected.

## View and use synonyms

Each disease and finding name may have synonyms, which the software also checks in search mode. To see the synonyms for a particular finding or disease hover your mouse over the button. The results display as shown here.

Figure 16: Viewing synonyms (basic mode)

The screenshot shows the SimulConsult software interface. At the top, there are navigation tabs: "Initial", "Diagnose", "Profile", "Assess", and "Tips". Below the navigation, there are buttons for "Differential", "Add findings", and "Add tests". The main area displays a patient profile for a "2 year old boy". The profile includes a "Phenotype" section with a green "4" and a red "1". The findings are categorized into "Pertinent positive findings" and "Pertinent negative findings".

**Pertinent positive findings:**

- Nystagmus, microcephalic, microencephalic, microencephaly, dwarfism
- Hyperreflexia
- Microcephaly
- CT or MRI: pan-cerebellar atrophy or hypoplasia

**Pertinent negative findings:**

- Regression

A tooltip is visible over the "Microcephaly" finding, displaying the following text: "Explanatory terms: <3rd %ile; small head; OFC, percentile, head circumference, microcranium, microcephalic, microencephalic, microencephaly, dwarfism".

## VIEW THE DIFFERENTIAL DIAGNOSIS

After entering the initial findings, you can go to the differential diagnosis screen by pressing the “Differential diagnosis” button (see previous figure). From there you can add further findings to narrow the differential diagnosis.

Figure 17: Differential Diagnosis

SimulConsult Initial Diagnose Profile Assess Tips

Differential Add findings Add tests Phenotype 5 2 Genotype

**Probability:**

- Aicardi-Goutières syndrome, AR
- PCH2: pontocerebellar hypoplasia 2
- PCH8: pontocerebellar hypoplasia, CHMP1A-related
- PCH10: pontocerebellar hypoplasia, CLP1-related
- CDG1A: PMM2-related
- LIS2: RELN-related lissencephaly, AR
- Vici syndrome
- Neurodevelopmental disorder with cerebellar atrophy and with or without seizures
- PCH1B: pontocerebellar hypoplasia, EXOSC3-related
- PCH9: pontocerebellar hypoplasia, AMPD2
- PCH1A: pontocerebellar hypoplasia, VRK1-related
- PEHO syndrome
- VLDLR-related cerebellar hypoplasia

# ADD FINDINGS BASED ON USEFULNESS

One of the key ways to use SimulConsult is on the diagnose screen with either the clinical finding or test results tabs. The software provides suggestions based on usefulness in narrowing the differential.

## Add Useful Clinical Findings

Figure 18: Add clinical findings based on usefulness

The screenshot shows the SimulConsult software interface. At the top, there are navigation tabs: 'Initial', 'Diagnose', 'Profile', 'Assess', and 'Tips'. Below these are sub-tabs: 'Differential', 'Add findings', 'Add tests', 'Phenotype' (with a '5' in a green circle and a '2' in a red circle), and 'Genotype'. The 'Add findings' tab is active. On the left, a list of clinical findings is shown, including 'Aicardi-Goutières sy...', 'PCH2: pontocerebell...', 'PCH8: pontocerebell...', 'PCH10: pontocerebell...', 'CDG1A: PMM2-related', 'LIS2: RELN-related li...', 'Vici syndrome', 'Neurodevelopmental...', 'PCH1B: pontocerebell...', and 'PCH9: pontocerebell...'. Below this list are 'Top', '<', '1', and '>' buttons. The main area is titled 'Findings by usefulness' and contains the text 'Top findings ranked by usefulness in narrowing the differential diagnosis'. There are two radio buttons: 'Usefulness in all diseases' (selected) and 'Rule in or out selected disease'. Below this is a list of findings with progress bars: 'Modifier: Truncal nature to hypotonia', 'Weakness, significant', 'Modifier: Recurrent exacerbations', 'Retroflexion of neck, tonic or fixed', 'Jitteriness or generalized clonus' (highlighted with a green border), 'Modifier: Spasticity character to hypertonia', 'Hypotonia', 'Hypertonia / stiffness', and 'Dystonia'. At the bottom, there are 'Top', '<', '1 of all findings', and '>' buttons.

## Add Useful Test Results

Here you can add test results you have, and you can learn which ones might be useful. The usefulness considers how much the result will narrow the differential diagnosis, and also, cost and any danger to the patient. It prioritizes low cost safe tests, where the results will make a difference.

Figure 19: Add useful test results

The screenshot shows the SimulConsult interface. At the top, there are navigation tabs: Initial, Diagnose, Profile, Assess, and Tips. Below this, there are sub-tabs: Differential, Add findings, Add tests (selected), Phenotype (with a red '4' and '1' indicator), and Genotype. On the left side, there is a vertical list of conditions, each in a blue-bordered box: Aicardi-Goutières syndro..., SCAR2: Spinocerebellar a..., PCH2: pontocerebellar hy..., Angelman syndrome, Galloway-Mowat syndrom..., CMV, symptomatic conge..., HLD1: Pelizaeus-Merzbac..., CDG1A: PMM2-related, LIS2: RELN-related lissen..., Mevalonic aciduria, infantile, Neurodevelopmental diso..., HLD6: hypomyelinating le..., and Marinesco-Sjögren syndr... The main area is titled 'Tests by usefulness' and contains a list of tests ranked by their usefulness. Each test entry includes a 'Bundle' dropdown menu, a test name, and a horizontal bar chart showing the test's usefulness score. The tests listed are: CT scan of the brain, MRI scan of the brain, UA (urinalysis), Proteinuria, Albumin low in serum, X-ray or CT: brain calcifications, Modifier: Nephrotic degree to proteinuria, Creatine kinase high, ABR abnormal, WBC high in CSF, and CT or MRI: cerebral cortex atrophy or hypoplasia. An 'All tests' dropdown is located in the top right corner of the test list.

## Rule in or out a specific disease

Sometimes you want to rule in or out a disease high in the differential diagnosis. To do so, click to select the disease, and then you will be offered (on both Add findings and Add tests) the option to “Rule in or out selected disease” rather than the default of “Usefulness in all diseases”.

Figure 20: Use Rule in or out selected disease to narrow differential diagnosis

The image shows two screenshots of the SimulConsult web application interface. The top screenshot shows the 'Add findings' tab with the 'Usefulness in all diseases' radio button selected. The bottom screenshot shows the same interface with the 'Rule in or out selected disease' radio button selected, and a larger list of findings is visible.

**SimulConsult** Initial Diagnose Profile Assess Tips

Differential **Add findings** Add tests Phenotype 4 1 Genotype

**Findings by usefulness**  
Top findings ranked by usefulness in narrowing the differential diagnosis

Usefulness in all diseases  Rule in or out selected disease

Findings	Usefulness
Ataxia	High
Weakness, significant	Medium
Dystonia	High

**SimulConsult** Initial Diagnose Profile Assess Tips

Differential **Add findings** Add tests Phenotype 4 1 Genotype

**Findings by usefulness**  
Top findings ranked by usefulness in narrowing the differential diagnosis

Usefulness in all diseases  Rule in or out selected disease

Findings	Usefulness
Ataxia	High
Weakness, significant	Medium
Dystonia	High
Gait abnormality	Medium
Modifier: Spasticity character to hypertonia	Medium
Dysarthria or abnormal sound character	Medium
Weight low or weight loss	Medium
Hypotonia	Medium
Retroflexion of neck, tonic or fixed	Medium
Stature short	Medium
Dysphagia or feeding difficulty	Medium
Hypertonia / stiffness	Medium
Tremor of limbs, trunk or head	Medium
Choreoathetosis	Medium
Seizures with abnormal movements	Medium

## VIEW THE FINDINGS ALREADY ENTERED

To see the findings entered about this case, and their pertinence to the differential, click the “**Phenotype**” tab. The numbers on the tab indicate the pertinent positive and negative finding count already entered.

Note that by clicking the onset, one can always “un-specify” the finding to eliminate it from the patient findings by choosing “Not specified”.

A mathematical representation of the common medical concept of “Pertinence” (as used in “pertinent positives and negatives”) is represented by the green shading overlay on the patient’s findings. Usefulness and pertinence are related concepts: pertinence is retrospective and usefulness prospective.

Figure 21: Phenotype of the patient

SimulConsult Initial Diagnose Profile Assess Tips

Differential Add findings Add tests **Phenotype** 4 1 Genotype

**2 year old boy**

**Pertinent positive findings**

* ▾	≤1m ▾	Nystagmus, non-rotary
* ▾	≤6m ▾	Hyperreflexia
* ▾	@1m ▾	Microcephaly
* ▾	✓ ▾	CT or MRI: pan-cerebellar atrophy or hypoplasia

**Pertinent negative findings**

X ▾	Regression
-----	------------

Aicardi-Goutières syndr...  
PCH2: pontocerebellar ...  
Angelman syndrome  
CDG1A: PMM2-related  
LIS2: RELN-related lisse...  
Galloway-Mowat syndro...  
SCAR2: Spinocerebellar ...  
Mevalonic aciduria, infa...

### TIP

The higher the pertinence of the entered findings, the more important it is for you to be sure that the finding is reliably determined – since the high pertinence findings are (by definition) driving the diagnosis.

## Get back to the “Core finding lists” and other search modes

To return to Core finding lists or any of the other methods typically used for entering initial findings, click the search icon.

## Contextual links

When you click on either the disease or finding, you can then access links to various resources with “Tips” at the top. Illustrated here is Vici Syndrome, and a link to a OJRD article and to OMIM. Since the last finding entered was Regression, one gets tips related to the finding. Clicking on a finding, and then Tips, gets Tips for the selected finding.

Regular sources include GeneReviews, OMIM (Online Mendelian Inheritance in Man), Orphanet, as well as many individual test books and articles. Links to disease associations, and various useful calculators are also included.

Figure 22: The user can click on a disease to show disease-related links

The screenshot displays the SimulConsult web application interface. At the top, there is a navigation bar with the SimulConsult logo and menu items: Initial, Diagnose, Profile, Assess, and Tips. Below the navigation bar, there are several tabs: Differential, Add findings, Add tests, Phenotype (with a green circle containing '5' and a red circle containing '2'), and Genotype. The 'Differential' tab is active, showing a list of conditions under the heading 'Probability:'. The conditions listed are: Aicardi-Goutières syndrome, AR; PCH2: pontocerebellar hypoplasia 2; PCH8: pontocerebellar hypoplasia, CHMP1A-related; PCH10: pontocerebellar hypoplasia, CLP1-related; CDG1A: PMM2-related; LIS2: RELN-related lissencephaly; Vici syndrome; Neurodevelopmental disorder with pontocerebellar hypoplasia; PCH1B: pontocerebellar hypoplasia; PCH9: pontocerebellar hypoplasia; PCH1A: pontocerebellar hypoplasia; PEHO syndrome; and VLDLR-related cerebellar hypoplasia. The 'Vici syndrome' entry is highlighted. A browser window is overlaid on the right side of the page, showing the URL 'simulconsult.com/soon/tips'. The browser window displays the 'Tips about disease' section for 'Vici syndrome', which includes links to 'OMIM article' and 'OJRD: Vici syndrome'. Below this, there is a 'Tips about finding' section for 'Regression', which includes a link to 'SimulConsult resource: Details on judging regression'. A note at the bottom of the browser window states: 'Note: The color of the Tips navigation button indicates the information available: Blue = Disease only, Green = Finding only, White = Both, Grayed = Neither'.



## Profile Disease

If you click on a disease, you can get “Assess” and “Profile” screens.

**Profile disease** provides all the findings in a disease ranked by the frequency at the patient’s age. Using the “younger” and “older” will allow rapid scrolling of those frequency at different ages.

Figure 23: Profile Disease

The screenshot shows the SimulConsult interface for the 'Profile Disease' screen. The disease selected is 'Aicardi-Goutières syndrome, AR'. The interface includes a search bar, navigation buttons for 'Younger' and 'Older', and a table of findings. The table has columns for 'Require', 'Presence', 'Findings in this disease', and frequency bars for 'Gone' and 'Later' categories. The frequency bars are color-coded: black for 'Gone' and purple for 'Later'. The findings listed are:

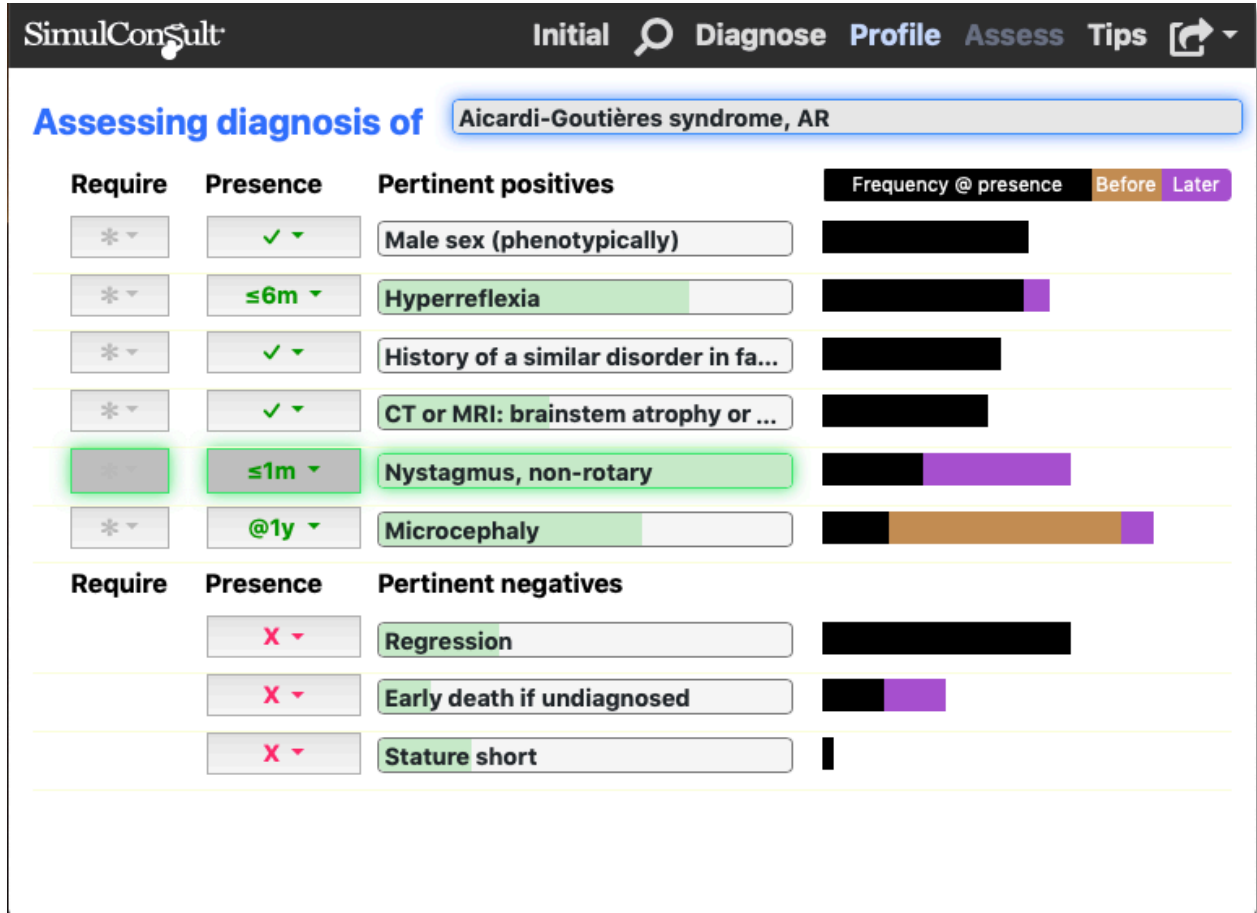
Require	Presence	Findings in this disease	Frequency @1 mo	Gone	Later
	? ▾	Interferon-α in the CSF elevated			
	? ▾	X-ray or CT: brain calcifications			
	? ▾	Modifier: Basal ganglia nature to ...			
	? ▾	Motor developmental delay			
	? ▾	Hypertonia / stiffness			
	? ▾	Modifier: Spasticity character to ...			
	? ▾	CT or MRI: cerebral cortex atroph...			
	? ▾	Retroflexion of neck, tonic or fixed			
	? ▾	MR Spectroscopy: lactate high in ...			

At the bottom of the interface, there are navigation buttons: 'Top', '<', '1 of 10', and '>'.

## Assess disease

**Assess disease** shows the fit of the patient's findings (positive and negative) with the disease. One can scroll down the differential to evaluate how good a case has been made for the diagnosis.

Figure 24: Assess Disease



## Profile finding

Similarly, if you click on a finding, you will be offered choices related to the finding selected. By clicking on Nystagmus the “Assess” and “Profile” options appear. The Profile is in all diseases and the Assess is in the differential.

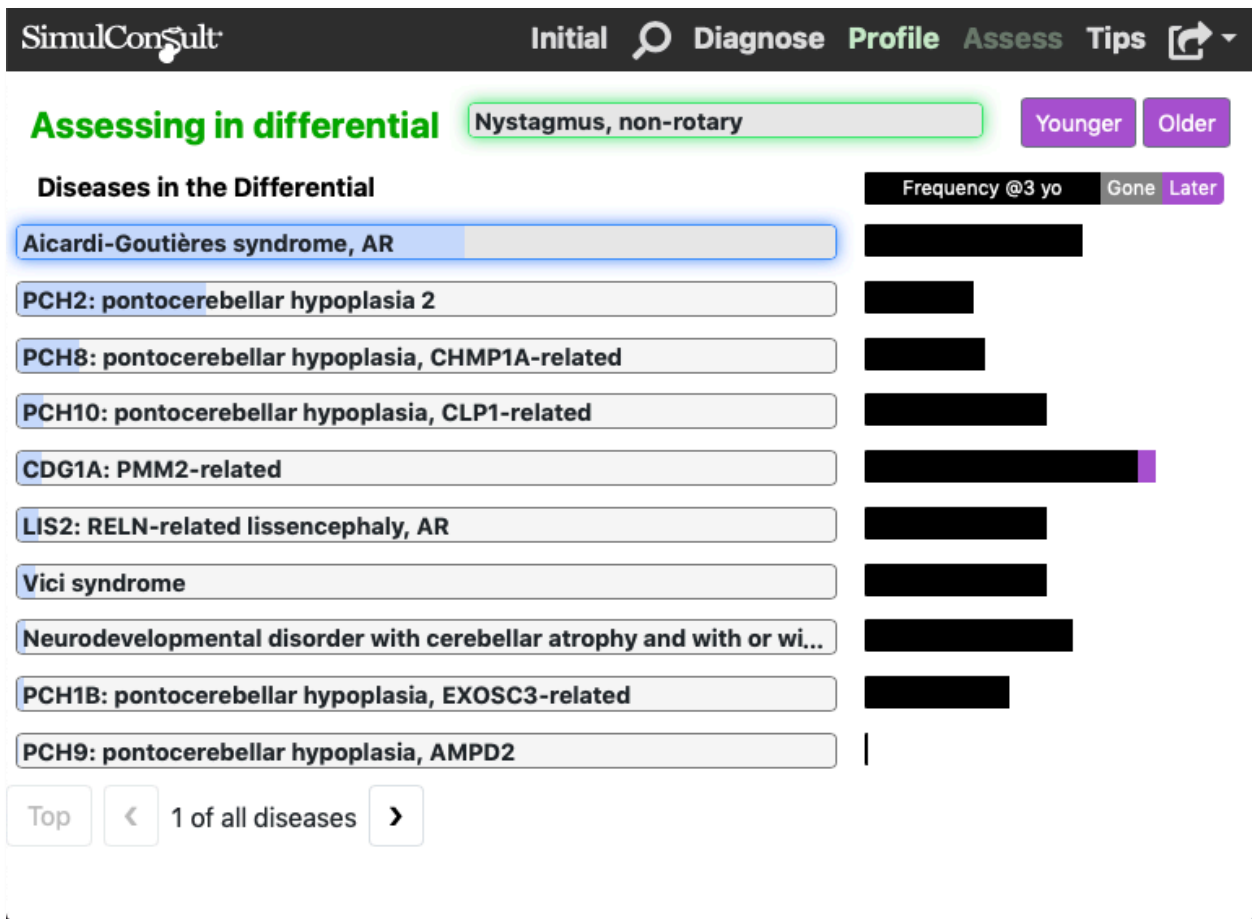
Figure 25: Profile Finding

The screenshot displays the SimulConsult interface. At the top, there is a navigation bar with the SimulConsult logo and tabs for 'Initial', 'Diagnose', 'Profile', 'Assess', and 'Tips'. The 'Profile' tab is currently selected. Below the navigation bar, the search bar contains the text 'Nystagmus, non-rotary'. To the right of the search bar are two buttons: 'Younger' (highlighted in purple) and 'Older'. Below the search bar, the section is titled 'Profile finding'. Underneath, there is a sub-section 'Diseases with this finding'. To the right of this list are two buttons: 'Frequency @3 yo' and 'Gone Later'. The list of diseases includes: Alström syndrome, GM2 gangliosidosis: Tay-Sachs disease, Nystagmus 1, congenital, X-linked, Idiopathic infantile nystagmus, non-FRMD7, Microphthalmia, cataract, and nystagmus, PAX6-related, Nystagmus 2, congenital, AD, HLD1: Pelizaeus-Merzbacher disease, classic, Lowe oculocerebrorenal syndrome, Nance-Horan cataract-dental syndrome, and ACHM7: achromatopsia, ATF6-related. Each disease name is in a light gray box, and to its right is a horizontal bar representing frequency. The bars for most diseases are black, while the bar for ACHM7 is purple. At the bottom left, there is a 'Top' button and a pagination control showing '< 1 of 63 >'.

## Assess finding

Assess finding looks at the frequency of the selected finding in the diseases in the differential diagnosis.

Figure 26: Assess finding



# SAVE AND REOPEN PATIENT HISTORY

## Output options

The software has three key outputs:

1. **Summary:** The Summary, a human readable “Informatics Lab Report” that provides a snapshot of the patient’s findings as they were entered and run against the database with a particular date stamp. The display includes the pertinence of each finding and the likelihood of each disease in the Differential Diagnosis, as well as recommended tests.
2. **Text string:** SimulConsult has created special codes (in the form of a text string) that allow you to reopen SimulConsult with the previously entered findings already present. (Note: In the version of SimulConsult accessed from the cloud, the Summary is machine-readable because it has the text string embedded in it).
3. **Note:** The Note is in the classic “subjective, objective, assessment, and plan” (SOAP) note format used in clinical medicine. In the version of SimulConsult accessed from the cloud, it outputs a file that can be copied and pasted into a medical record as plain text and then edited. It also contains the text string that can be saved. Note: since only medical professionals may have direct access to SimulConsult it is not advised to put the text string in the note, if notes are open to patient inspection, such as through Open Notes.

Figure 27: Saving your work or re-importing a saved patient



The screenshot shows the SimulConsult web application interface. At the top, there is a navigation bar with the SimulConsult logo and tabs for 'Initial', 'Diagnose', 'Profile', 'Assess', and 'Tips'. Below the navigation bar, there are several tabs: 'Differential', 'Add findings', 'Add tests', 'Phenotype' (with a '4' and a '1' indicator), and 'Genotype'. The 'Add findings' tab is active, showing a list of findings on the left and a 'Findings by usefulness' section on the right. The 'Findings by usefulness' section displays a list of findings ranked by usefulness, including 'Ataxia', 'Weakness, significant', 'Dystonia', 'Gait abnormality', and 'Modifier: Spasticity character to hypertonia'. A dropdown menu is open over the 'Phenotype' tab, listing options: 'Load or save patient', 'Chart note template', 'Summary report', 'Prognosis table for active disease', and 'Database'.

In addition, some coded outputs are possible within the Enterprise offerings.

# Save the “Summary”

Select “Summary report” and then download the PDF to save to your desktop or the EHR. Note: this produces a version that is both human readable and also can be reopened and read by the software.

Figure 28: Generating the Patient Summary

**Summary for the 2 year old boy with:**

**Pertinent positive findings**

Onsets can be at an age, by an age, or unknown

Req'd	Onset	Finding	Pertinence
	≤1m	Nystagmus, non-rotary	[Bar]
	≤6m	Hyperreflexia	[Bar]
	@1m	Microcephaly	[Bar]
✓		CT or MRI: pan-cerebellar atrophy or hypoplasia	[Bar]

**Pertinent negative findings**

Absent	Finding	Pertinence
X	Regression	[Bar]

**Differential diagnosis**

Disease	Probability
Aicardi-Goutières syndrome, AR	[Bar]
PCH2: pontocerebellar hypoplasia 2	[Bar]
Angelman syndrome	[Bar]
CDG1A: PMM2-related	[Bar]
LIS2: RELN-related lissencephaly, AR	[Bar]
Galloway-Mowat syndrome 3, OSGEP-related	[Bar]
SCAR2: Spinocerebellar ataxia, AR, congenital nonprogressive	[Bar]
Mevalonic aciduria, infantile	[Bar]
PCH8: pontocerebellar hypoplasia, CHMP1A-related	[Bar]
PCH10: pontocerebellar hypoplasia, CLP1-related	[Bar]
CMV, symptomatic congenital infection	[Bar]
Neurodevelopmental disorder with progressive microcephaly, spasticity, and brain anomalies	[Bar]
Peters plus syndrome	[Bar]
SCAR4: Spinocerebellar ataxia with saccadic intrusions	[Bar]
Pyruvate dehydrogenase E1α deficiency, early infantile	[Bar]
Neurodevelopmental disorder with cerebellar atrophy and with or without seizures	[Bar]
HLD15: leukodystrophy, hypomyelinating, EPRS-related	[Bar]
Rhizomelic chondrodysplasia punctata type 5	[Bar]
HLD1: Pelizaeus-Merzbacher disease, classic	[Bar]
Smith-Lemli-Opitz syndrome	[Bar]
Marinesco-Sjögren syndrome	[Bar]
CCFDN	[Bar]

Generated by SimulConsult® on 12 December 2018 13:18 using interface of 4 December 2018 9:42, algorithms of 10 December 2018 10:11 and database of 6 December 2018 13:13. All times are USA Pacific. Care setting was primary. Onset was used.

## Save the “text string”

Click **Load or save patient** and highlight the text in the bottom box to save it. Various APIs allow this information to be passed to other applications.

Figure 29: Load or save patient via a text string

The screenshot shows the SimulConsult interface with a dark header bar containing the logo and navigation links: Initial, Diagnose, Profile, Assess, and Tips. The main content area is divided into three sections:

- Summary File**
  - Load**: A text input field with the placeholder "(load a Summary Report in PDF or HTML format)" and a "Browse" button.
  - Text: "The Summary Report PDF has the information needed to resume the patient. The HTML version from the older version of the software can also be used."
  - Save**: A PDF icon with a red arrow pointing to a document.
- Variant File**
  - Load**: A text input field with the placeholder "(load a variant file)" and a "Browse" button.
- Patient Text String**
  - Load**: A large text area with the placeholder "Paste a patient text string here and click the Load Patient button". Below it is a "Load Patient" button.
  - Save**: A text area containing a long URL: `d=730&u=ftemp0&o=499999&u=ftemp158&o=399999&u=ftemp1&o=499999&u=ftemp20&o=b59&u=posner_2000_4_4_11_34_39&o=399999&u=ftemp220&o=b59&u=ftemp270&o=b269&i=1&t=c`. Below it is the text: "The Patient Text String above has the information needed to resume the patient."

## Save the “Note”

This generates the raw text for a classic note, although in list form rather than prose.

Figure 30: Saving the Note, with sections for History, Assessment and Plan

SimulConsult Initial Diagnose Profile Assess Tips

**CLINICAL NOTE INITIAL TEXT** (cut and paste as appropriate)

**HISTORY OF PRESENT ILLNESS**

This is a 2 year old boy with:

Nystagmus, non-rotary, onset by about 1 month old  
Microcephaly, onset by about 1 month old  
Hyperreflexia, onset by about 6 months old  
CT or MRI: pan-cerebellar atrophy or hypoplasia, present now  
Regression, absent

**Growth / development**

Microcephaly, onset by about 1 month old

**PHYSICAL EXAM**

**Present**

Nystagmus, non-rotary  
Hyperreflexia  
Microcephaly

**LAB / STUDIES**

**Present**

CT or MRI: pan-cerebellar atrophy or hypoplasia, present now

**ASSESSMENT**

This is a 2 year old boy with:

**Pertinent positives**

Nystagmus, non-rotary  
Hyperreflexia  
Microcephaly  
CT or MRI: pan-cerebellar atrophy or hypoplasia

**Pertinent negatives**

Regression

**Differential Diagnosis**

Aicardi-Goutieres syndrome, AR  
SCAR2: Spinocerebellar ataxia, AR, congenital nonprogressive  
PCH2: pontocerebellar hypoplasia 2  
Angelman syndrome  
Galloway-Mowat syndrome 3, OSGEP-related  
CMV, symptomatic congenital infection  
HLD1: Pelizaeus-Merzbacher disease, classic  
CDG1A: PMM2-related  
LIS2: RELN-related lissencephaly, AR  
Mevalonic aciduria, infantile  
Neurodevelopmental disorder with progressive microcephaly, spasticity, and brain anomalies  
HLD6: hypomyelinating leukodystrophy, TUBB4A -related  
Marinesco-Sjogren syndrome  
Pyruvate dehydrogenase E1alpha deficiency, early infantile  
Neurodevelopmental disorder with cerebellar atrophy and with or without seizures  
Galloway-Mowat syndrome 2, LAGE3-related  
PCH8: pontocerebellar hypoplasia, CHMP1A-related  
PCH10: pontocerebellar hypoplasia, CLP1-related  
Chromosome 18q deletion syndrome  
Peters plus syndrome  
Pyruvate dehydrogenase E1alpha deficiency, late infantile  
Ataxia-telangiectasia  
SCAR4: Spinocerebellar ataxia with saccadic intrusions  
GPIBD15: Glycosylphosphatidylinositol biosynthesis defect, GPAA1-related  
Smith-Lemli-Opitz syndrome

**PLAN**

**Most useful tests for this patient**

Bundle: CT scan of the brain  
Bundle: MRI scan of the brain  
Bundle: UA (urinalysis)



## Open previously saved findings

Some users separate the task of collecting and entering clinical findings from subsequent interpretation or sharing with the lab. The tasks may be divided among people or by time.

In some radiology and genomics labs, some users are exploring ways to get the referring clinician to submit the Patient Summary as part of the referral, so that the clinical picture can include the most robust information about findings. In any of these scenarios, as well as one where you just need to save your work and come back later, you can reopen a patient summary easily.

Figure 31: Load patient data

SimulConsult Initial Diagnose Profile Assess Tips


### Summary File

**Load**

(load a Summary Report in PDF or HTML format)

The Summary Report PDF has the information needed to resume the patient.  
The HTML version from the older version of the software can also be used.

**Save**

 PDF

### Variant File

**Load**

(load a variant file)

### Patient Text String

**Load**

Paste a patient text string here and click the Load Patient button

**Save**

d=730&u=ftemp0&o=499999&u=ftemp158&o=399999&u=ftemp1&o=499999&u=ftemp20&o=b59&u=posner\_2000\_4\_4\_11\_34\_39&o=399999&u=ftemp220&o=b59&u=ftemp270&o=b269&i=1&t=c

The Patient Text String above has the information needed to resume the patient.

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