SimulConsult®

A Simultaneous Consult On Your Patient's Diagnosis

Guide to Use of SimulConsult's Phenome Software

Table of contents

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 built its Phenome version to help solve this diagnostic problem, enabling clinicians to start with findings and get to the correct disease phenotype. 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 (the layman's view)

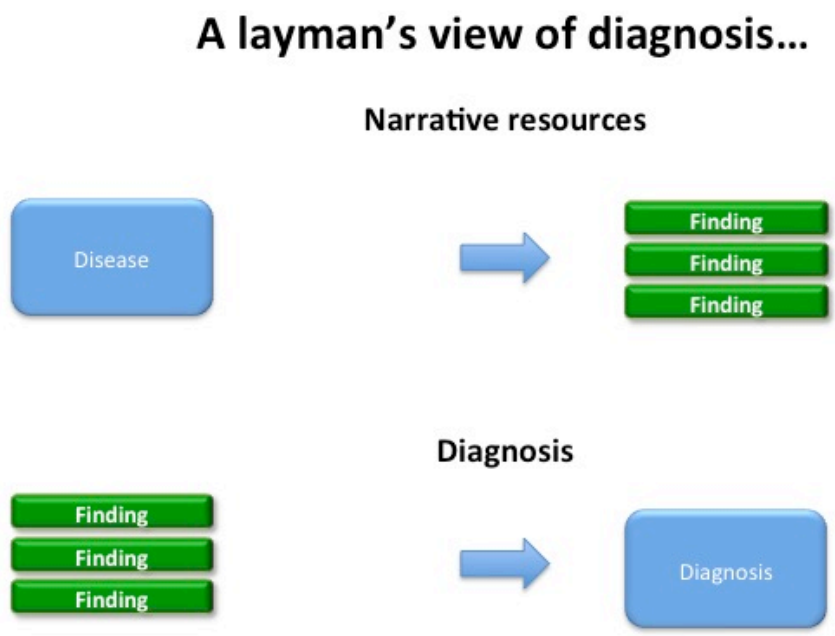
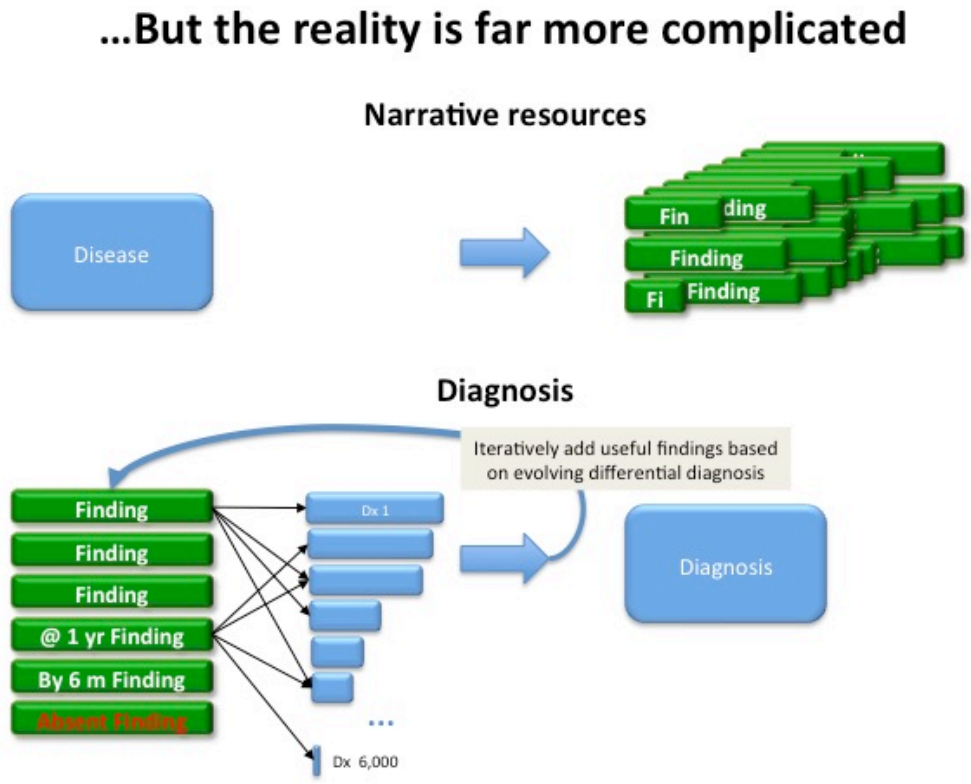


Figure 2: SimulConsult's core functionality: finding-based diagnosis that handles the full complexity



INTRODUCTION TO A FEW SIMULCONSULT CONVENTIONS

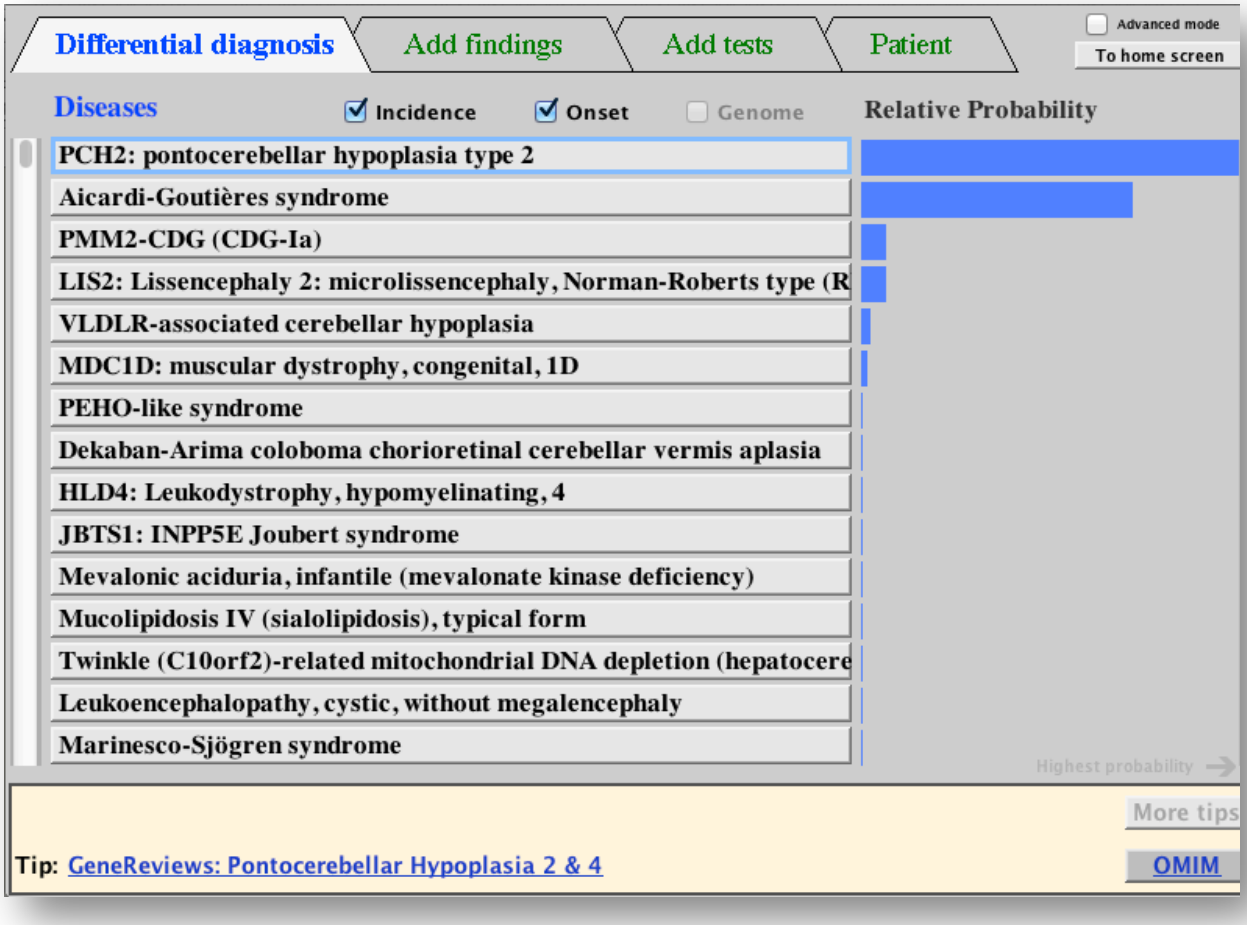
Colors and their meaning

Diseases are **blue**. Findings are **green.** Visited text turns **purple**, using the web convention for visited links. *Note: There are other colors used in the authoring and editing sections of the database.*

Contextual links

When you click on either the disease or finding you will see links to various resources at the bottom. Illustrated here is a link to a GeneReviews article and to OMIM. (Note: for Macintosh users: to get these outside links to work you'll need to follow a Macintosh link on the opening page of the software for instructions on settings needed).

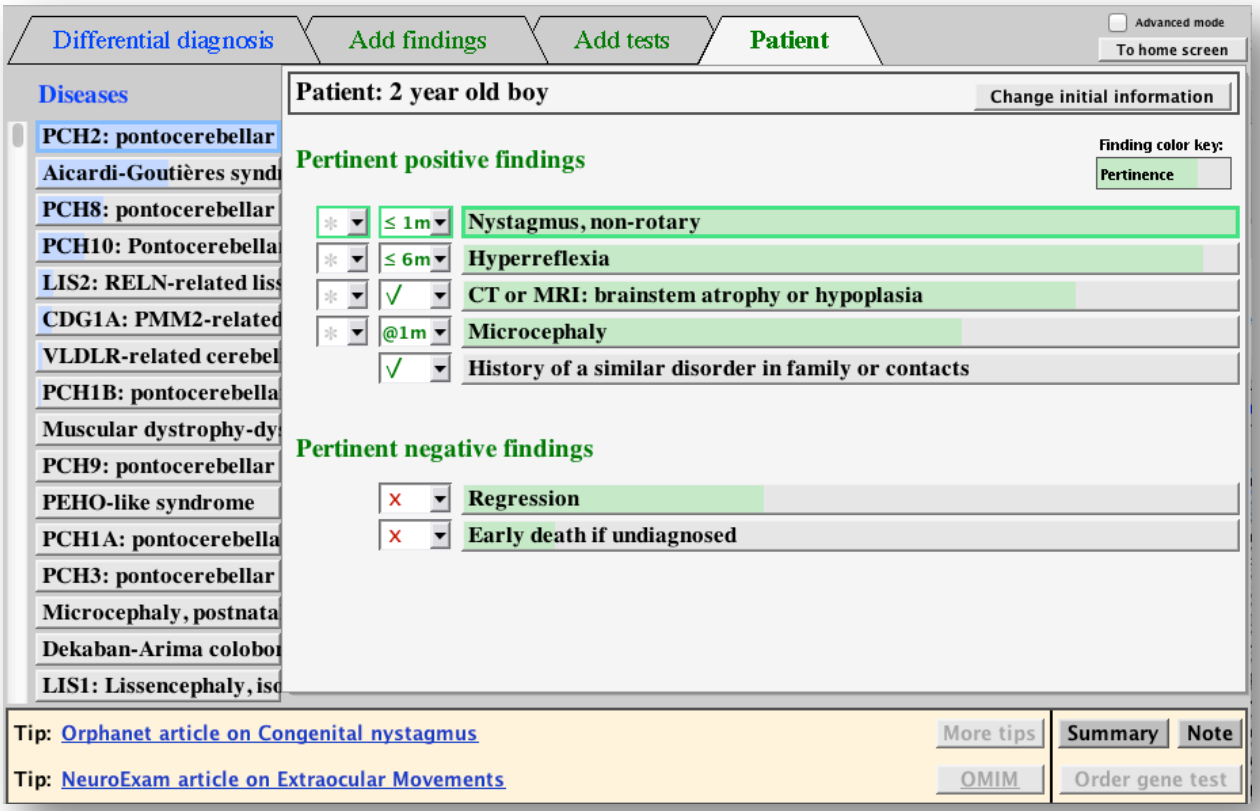
Figure 3: The user can click on a disease to show disease-related links



Regular sources include GeneReviews, OMIM (Online Mendelian Inheritance in Man), Orphanet, as well as many individual books and articles. Links to disease associations, and various useful calculators are also included. When there are many links, the "More tips" button will light up.

Similarly, when clicking on a finding, here **Nystagmus**, one gets tips related to the finding.

Figure 4: The user can click on a finding (clinical, test or gene) to show finding-based links

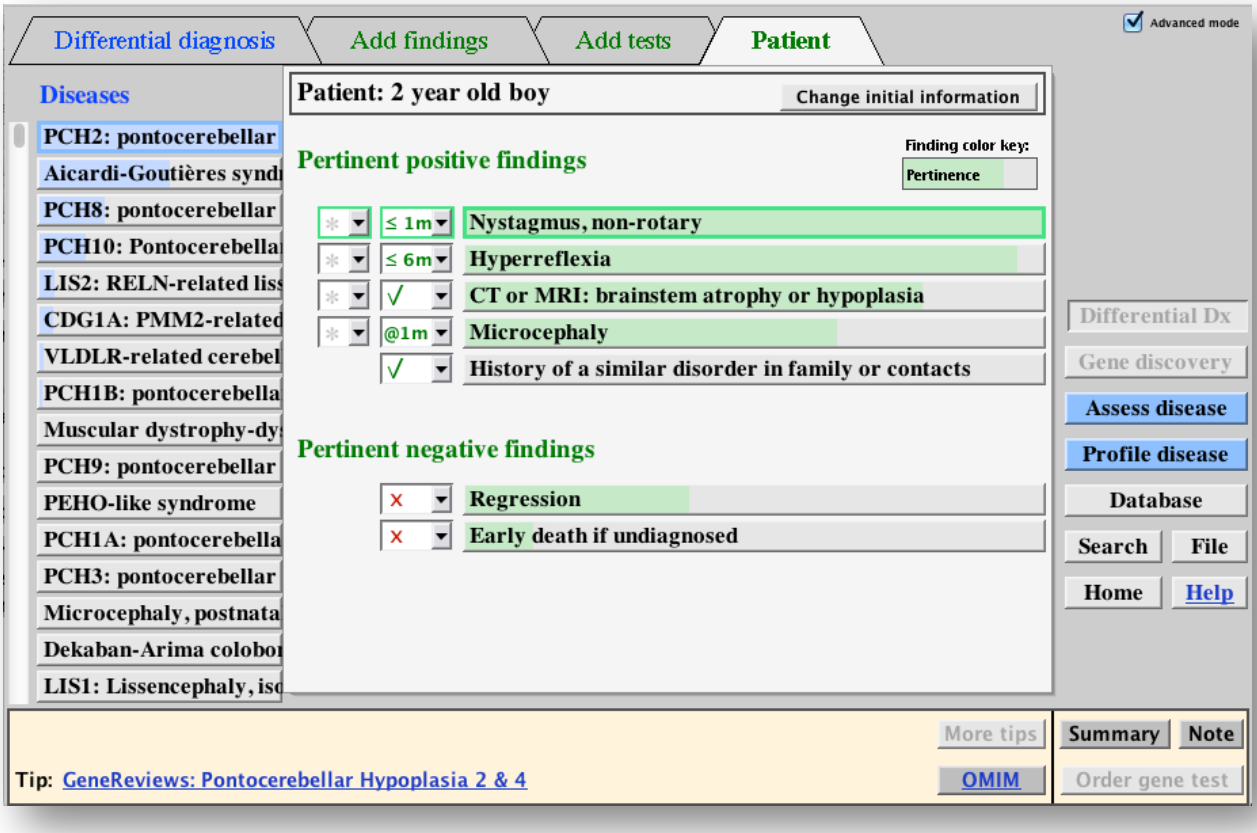


Contextual buttons in the advanced mode

When the advanced mode is selected (using the check box in the top right corner of the screen), more capabilities are available.

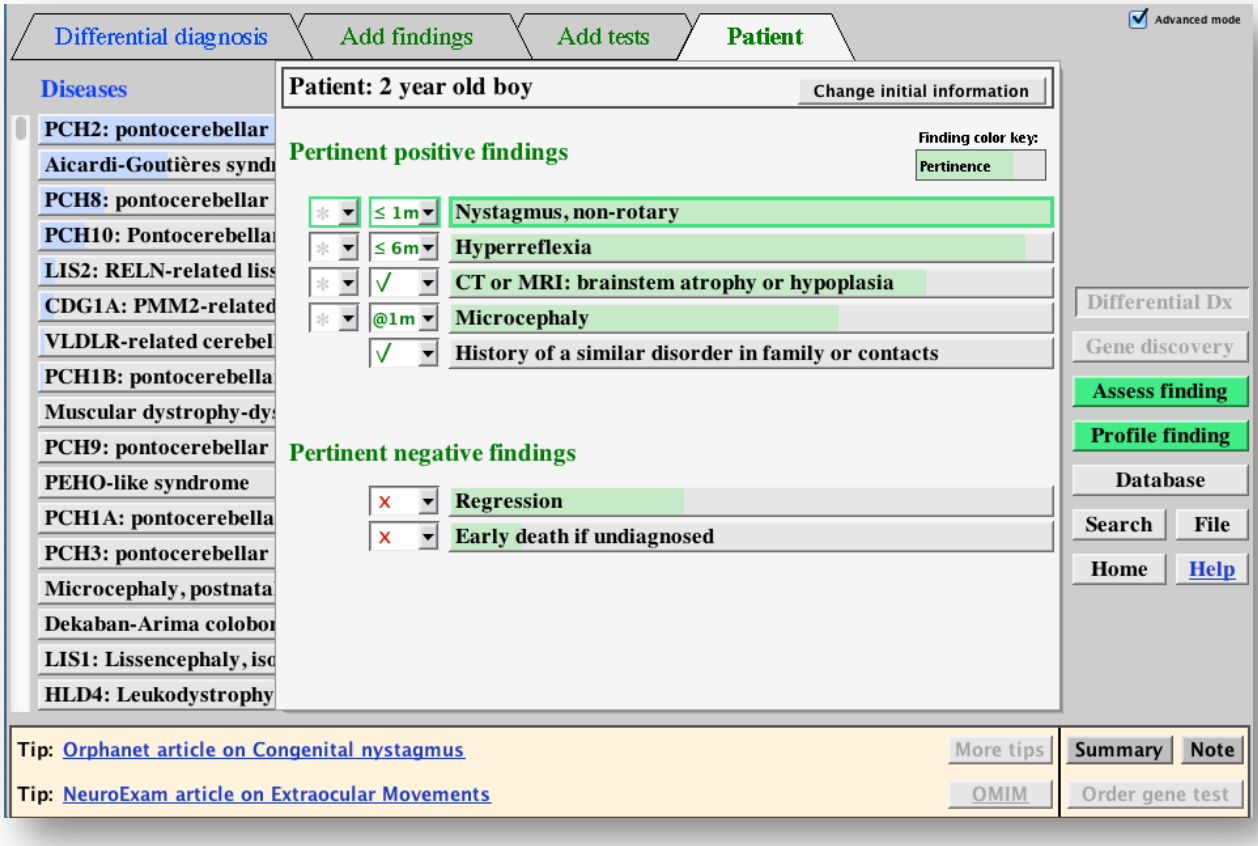
These buttons are contextual. If you click on a disease, you will be offered choices related to the disease selected. In this case, clicking on the blue button for the disease "PCH2: pontocerebellar …", the "**Assess disease**" and "**Profile disease**" buttons will turn blue to indicate they relate to a disease, here PCH2.

Figure 5: Disease-related buttons (in advanced mode)



Similarly, if you click on a finding, you will be offered choices related to the finding selected. By clicking on Nystagmus the "**Assess finding**" and "**Profile finding**" buttons will turn green to indicate that they relate to a finding, here Nystagmus.

Figure 6: Finding-related buttons (under advanced mode)



PATIENT CASE USED FOR ILLUSTRATIONS

This 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 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

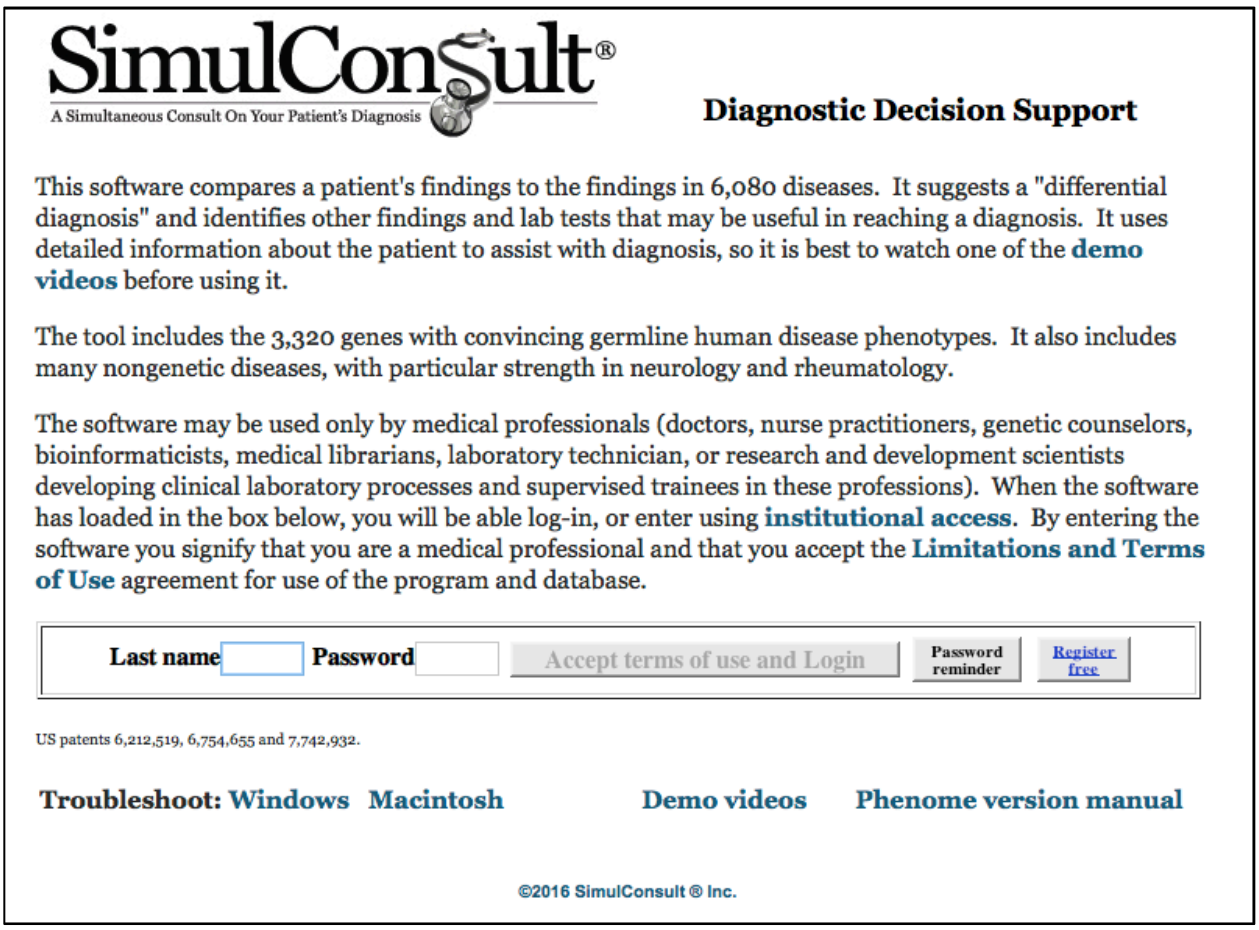
GET ACCESS

1. Individual Cloud-accessed version

Click **"Go to Login"** at **www.SimulConsult.com and then either:**

Individual log-in with last name and password

Figure 7: Individual Access



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

2. Institutional access as a result of your IP address being recognized

In a library subscription, the software is made available through IP access.

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

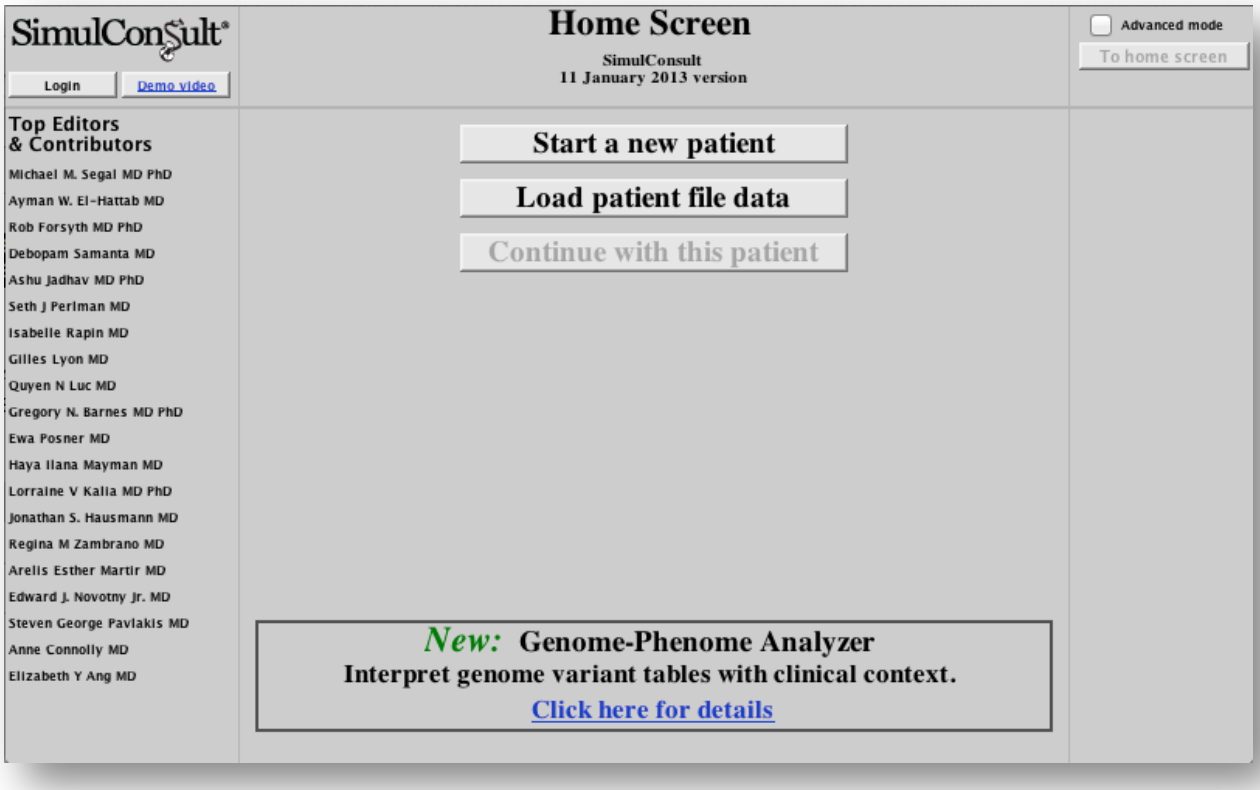
*If you have the **electronic health record or laboratory information system integrated version**, please see the companion document for how to launch SimulConsult from within your system.*

BEGIN BY ENTERING THE PATIENT AGE AND SEX

From Cloud version, start a new patient, then enter age and gender

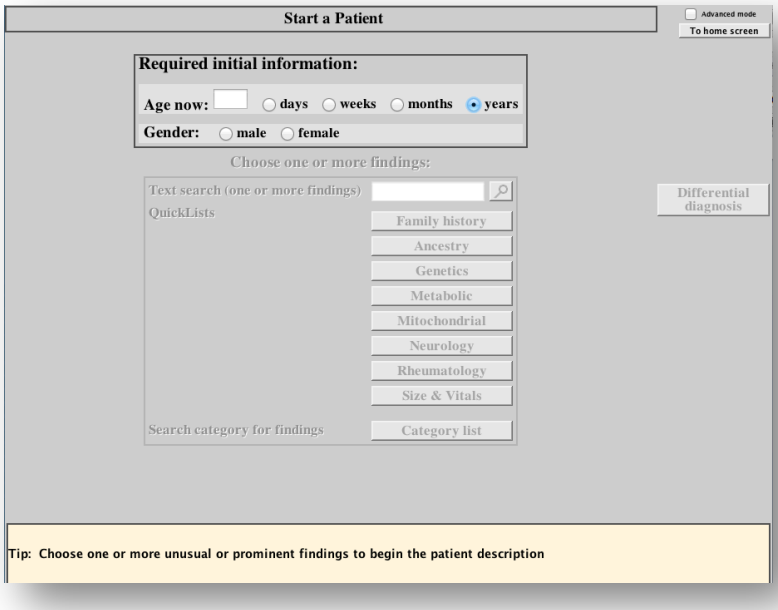
Click the "**Start a new patient**" button.

Figure 8: Start a new patient



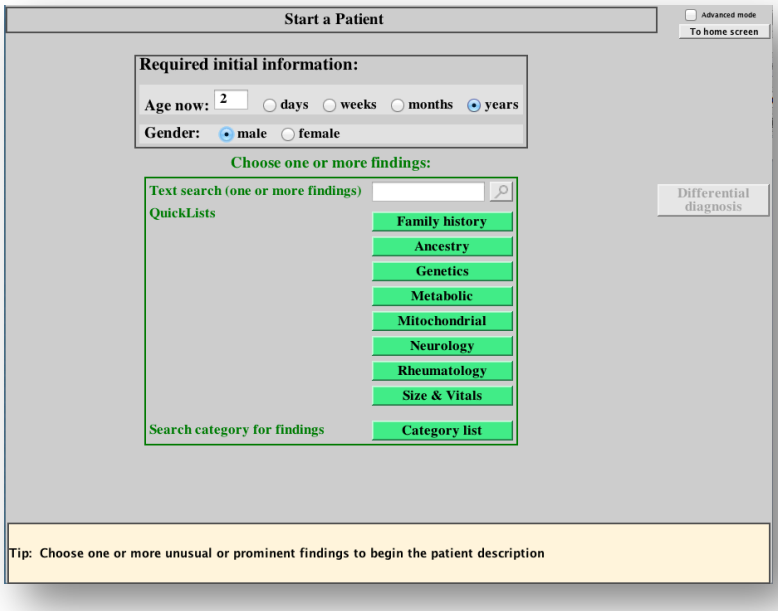
The first step is to enter the age and gender. Once that is entered, choices will appear for how to enter findings.

Figure 9 a & b: Entering the patient age and gender then offers choices for how to enter findings



Starting from the enterprise version

The age and gender information comes in automatically and you start here.



ENTER INITIAL KEY FINDINGS, USING DIFFERENT SEARCH MODES

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).

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

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.

The importance of requiring certain findings

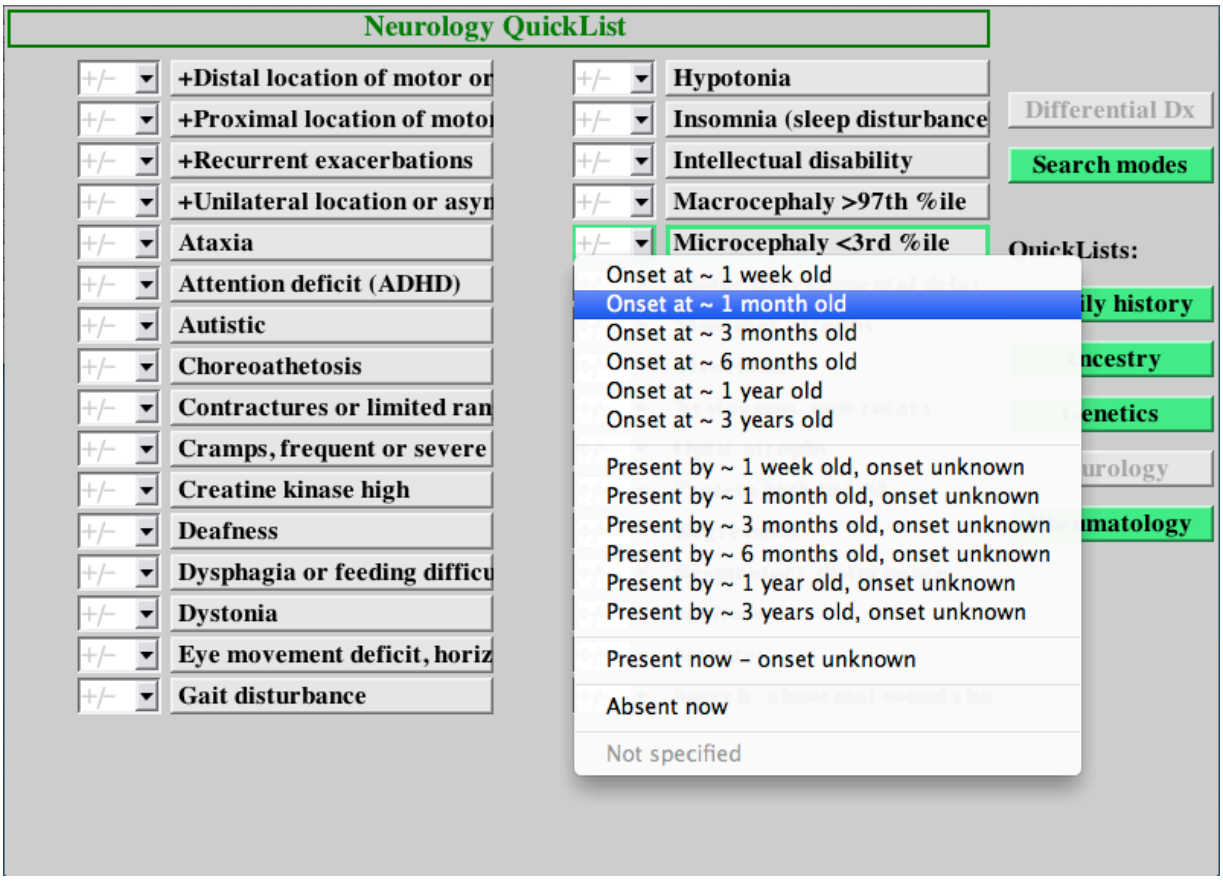
The default in the software is to take into account the possibility that a finding is not related to the primary diagnosis; the software has extensive probability information to make these assessments. However, when a common finding is particularly notable, such as a very high creatine kinase level,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

How to enter a finding: onset, presence or absence

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 10: How to enter a finding



Modes for entering initial findings

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

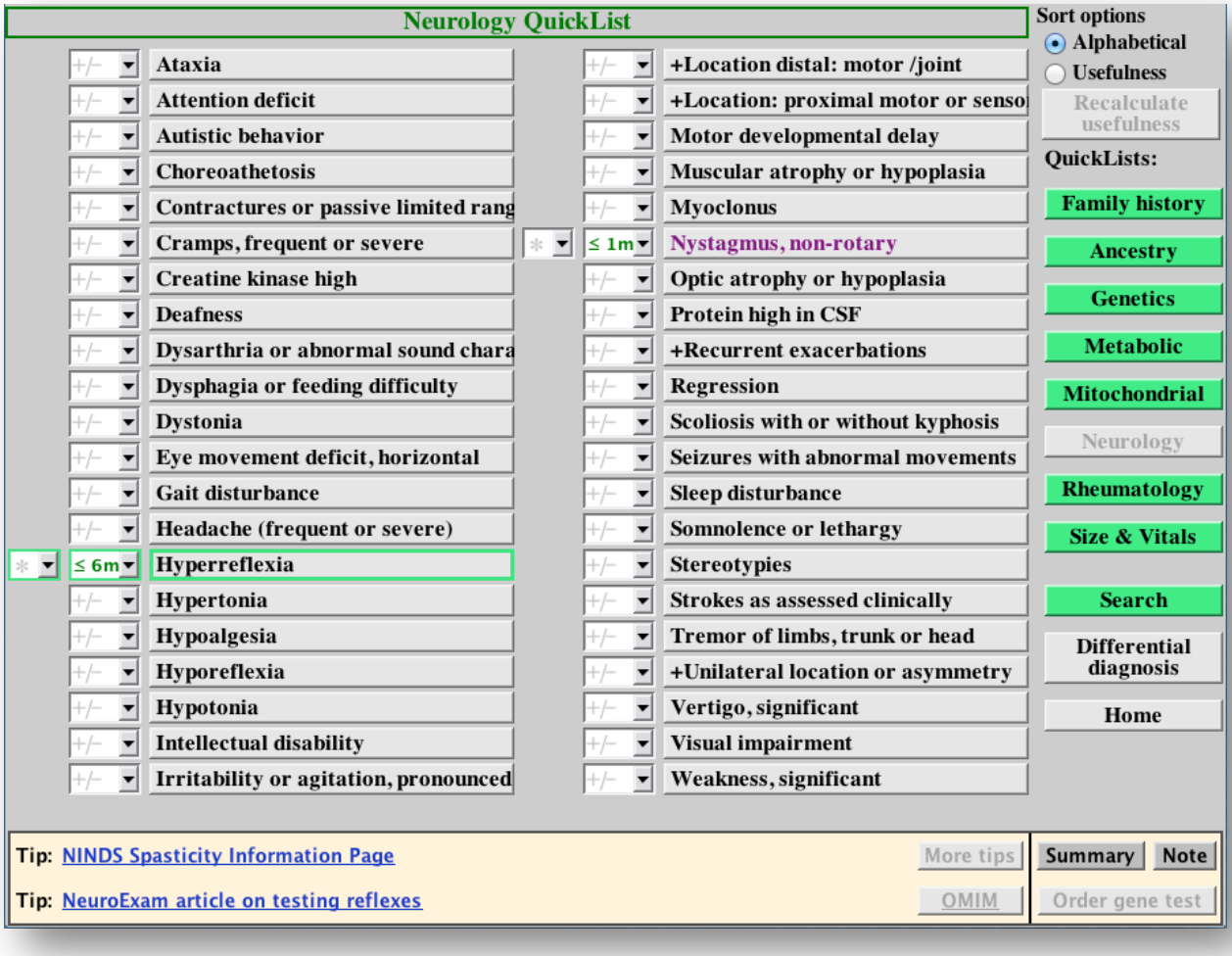
1. **QuickLists** (common findings in genetics, neurology, rheumatology and ancestry, as well as an interface for family history)
2. **Categories** (e.g., Cardiac & vascular)
3. **Search** (one or more terms)

Note: Once you have an initial differential diagnosis, the Useful findings and Useful tests tabs will often be the most convenient way to add findings.

Enter using “QuickLists”

Using the “**Neurology QuickLists**” and “**Family History**”, you can add a set of pertinent positives and negatives.

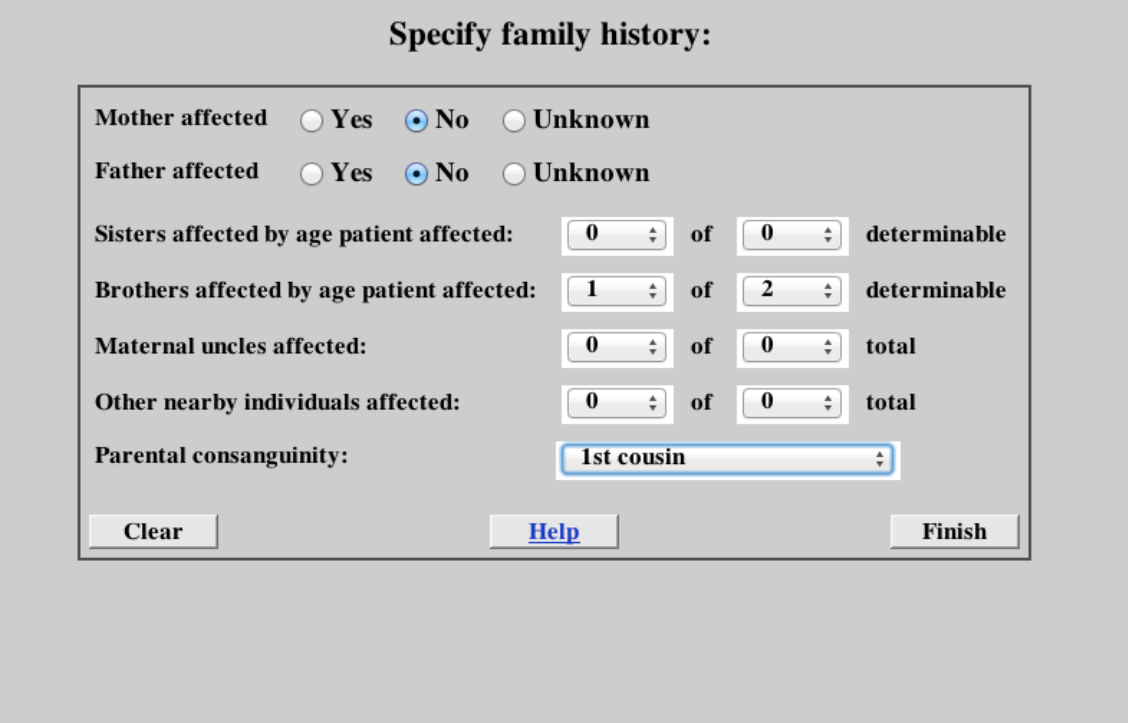
Figure 11: Entering findings using the Neurology QuickLists



Notice that the list can be sorted alphabetically, as shown here by selecting the sort option in the top right, or in order of usefulness of these findings in narrowing the differential diagnosis, which is relevant once some findings have been entered.

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

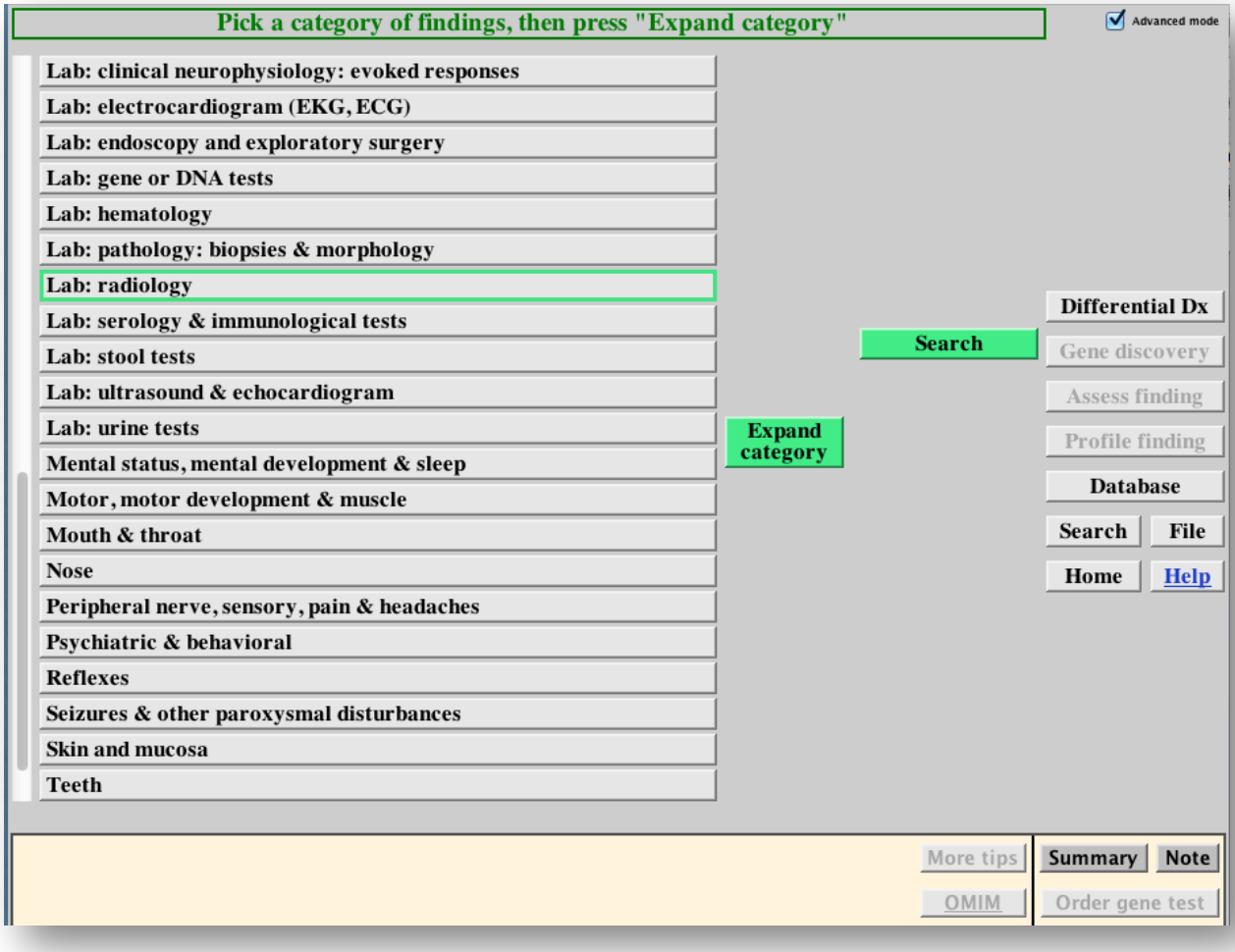
Figure 12: Entering family history using the QuickList



Enter using “Categories” of findings

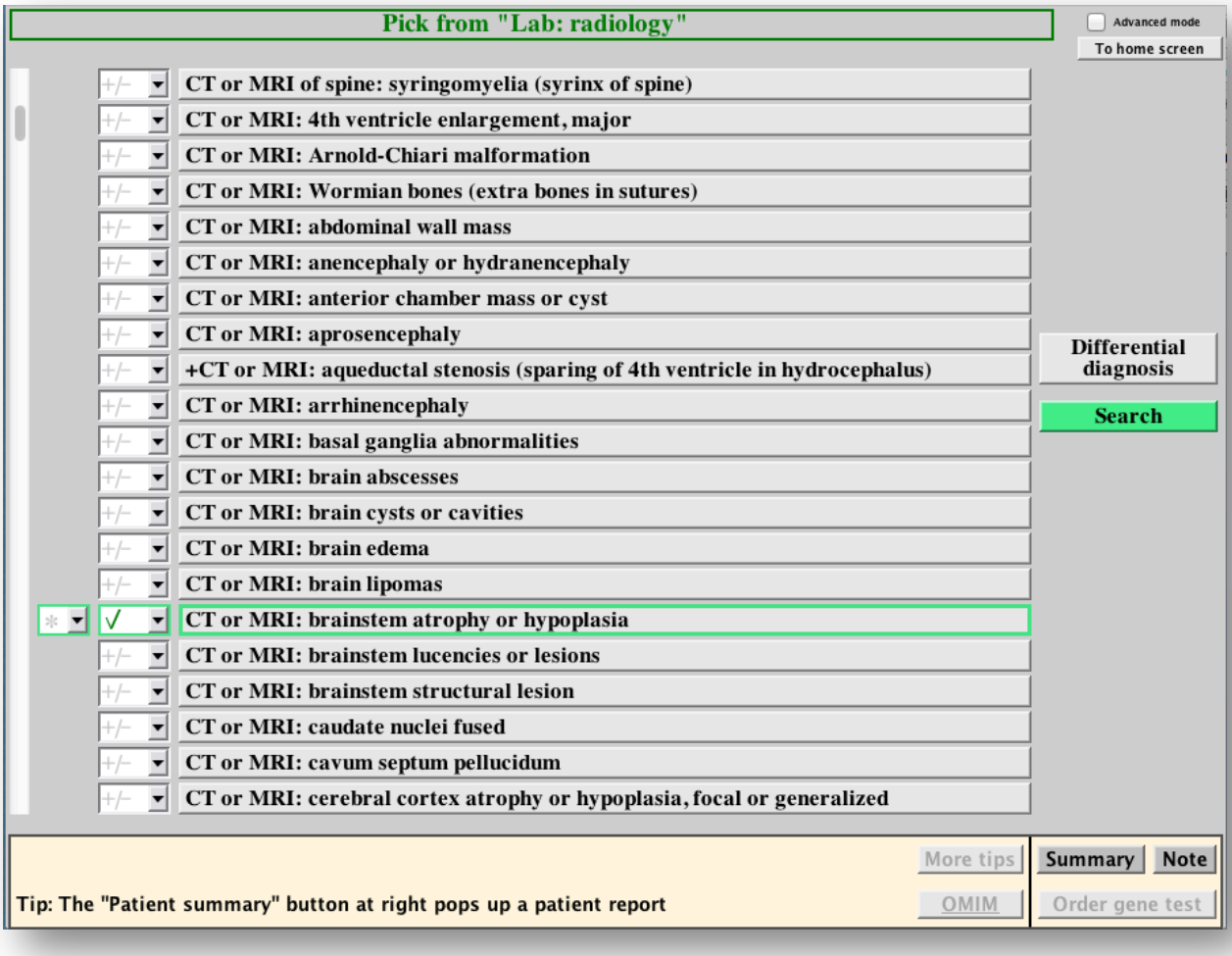
Select “**Lab: radiology”** in the “**Category of findings”**.

Figure 13: Using categories (advanced mode)



By clicking on "**Lab: radiology**" and then "**Expand category**", we can scroll down to find "CT or MRI: brainstem atrophy or hypoplasia" and enter that it is present with onset unknown.

Figure 14: Entering findings using Categories (advanced mode)



Enter using search

You can always search on terms, and 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 15: Entering findings using search (basic mode)

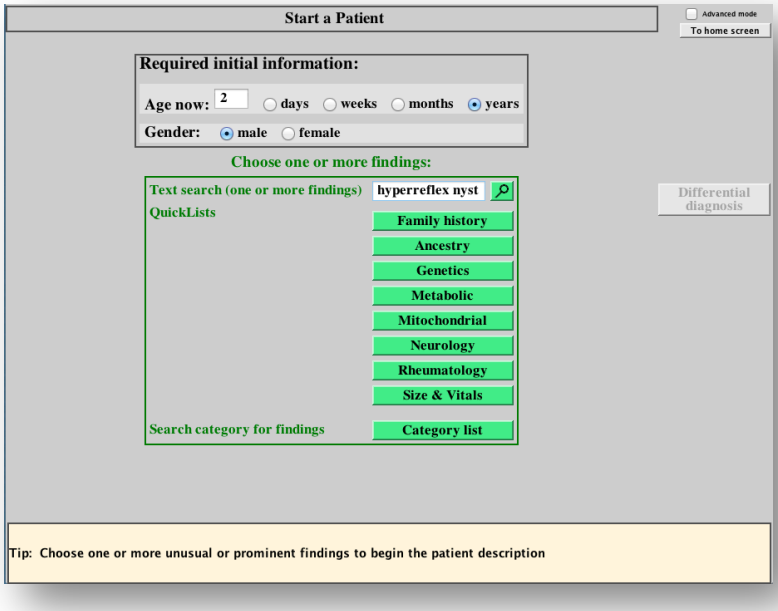
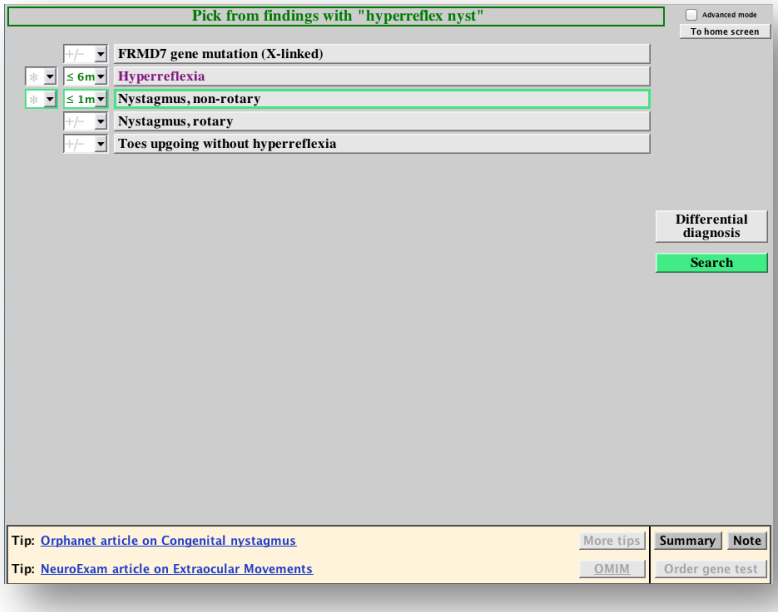


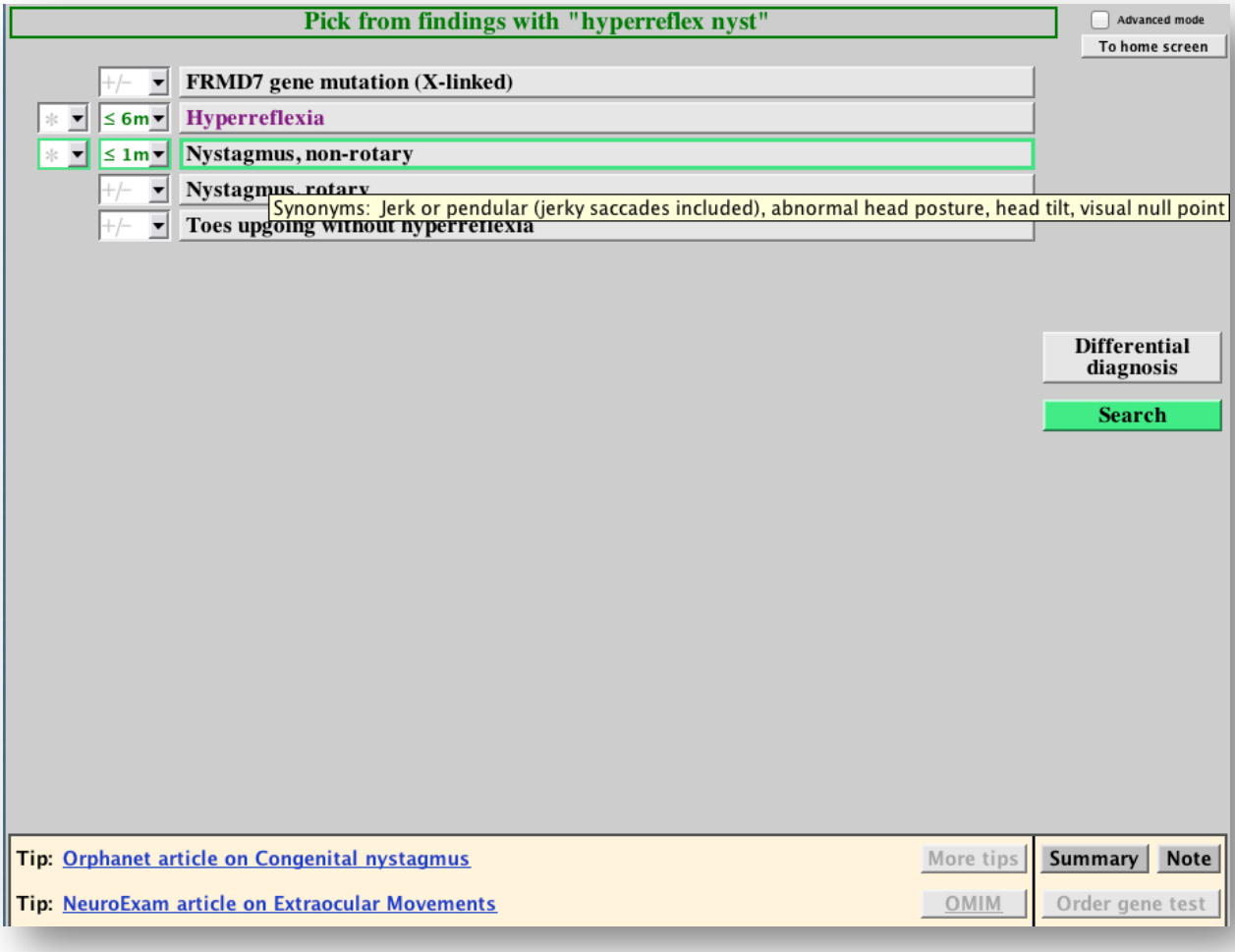
Figure 16: Selecting from the search results to define onset (basic mode)



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 in a yellow "tool tip" box as shown here.

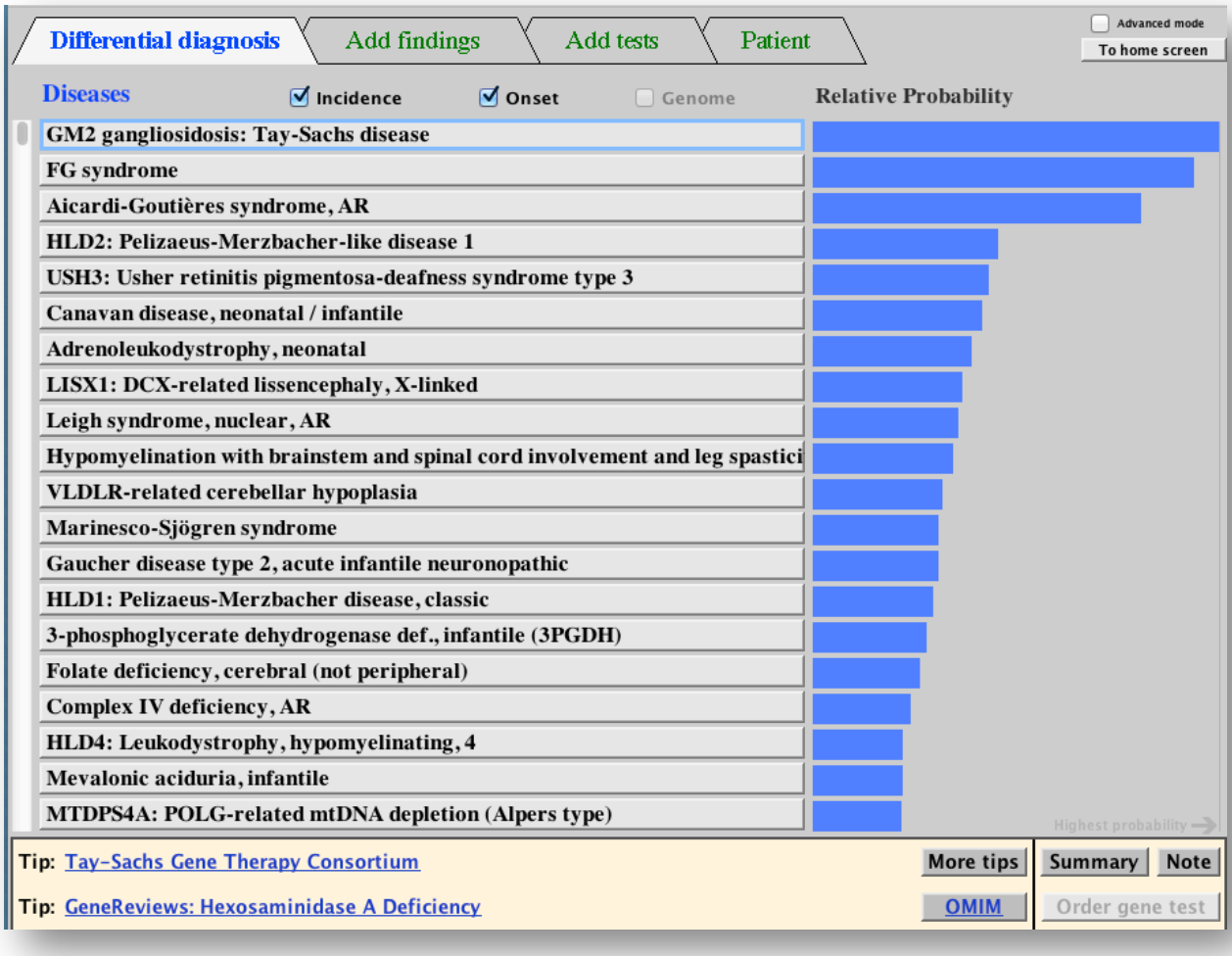
Figure 17: Viewing synonyms (basic mode)



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 18: Differential Diagnosis

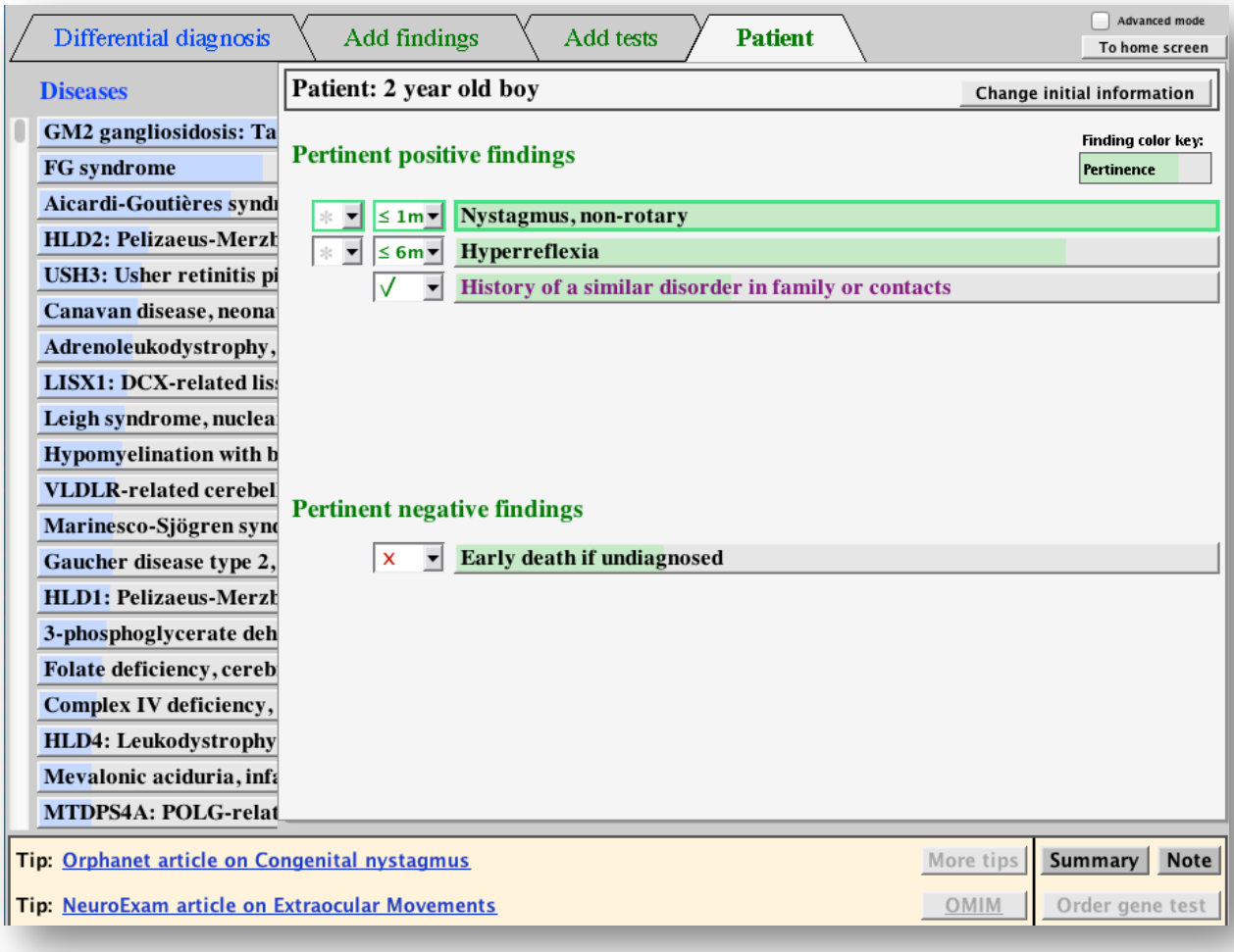


VIEW THE FINDINGS ALREADY ENTERED

To see the findings we have entered about this case, and their pertinence to the differential, click the "**Patient"** tab from the **Differential Diagnosis** section. 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.

Figure 19: The Patient Tab



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.

ADD FINDINGS TO NARROW THE DIFFERENTIAL DIAGNOSIS

After entering the initial findings you have more methods to add findings to narrow the differential diagnosis, illustrated below:

1. **Add findings** and **Add tests** tabs, which provide a list of findings ranked in order of which will be ***most useful*** in narrowing the evolving differential diagnosis.
    a. When adding tests, you have the choice to view a "bundle" of test results that could result from ordering a single test, such as an MRI.
2. The **Disease profile** (select the Advanced mode to get this option) to enter findings about the disease you suspect
3. **Search** button in the Add findings or Add tests tabs to return to the options available under the initial findings

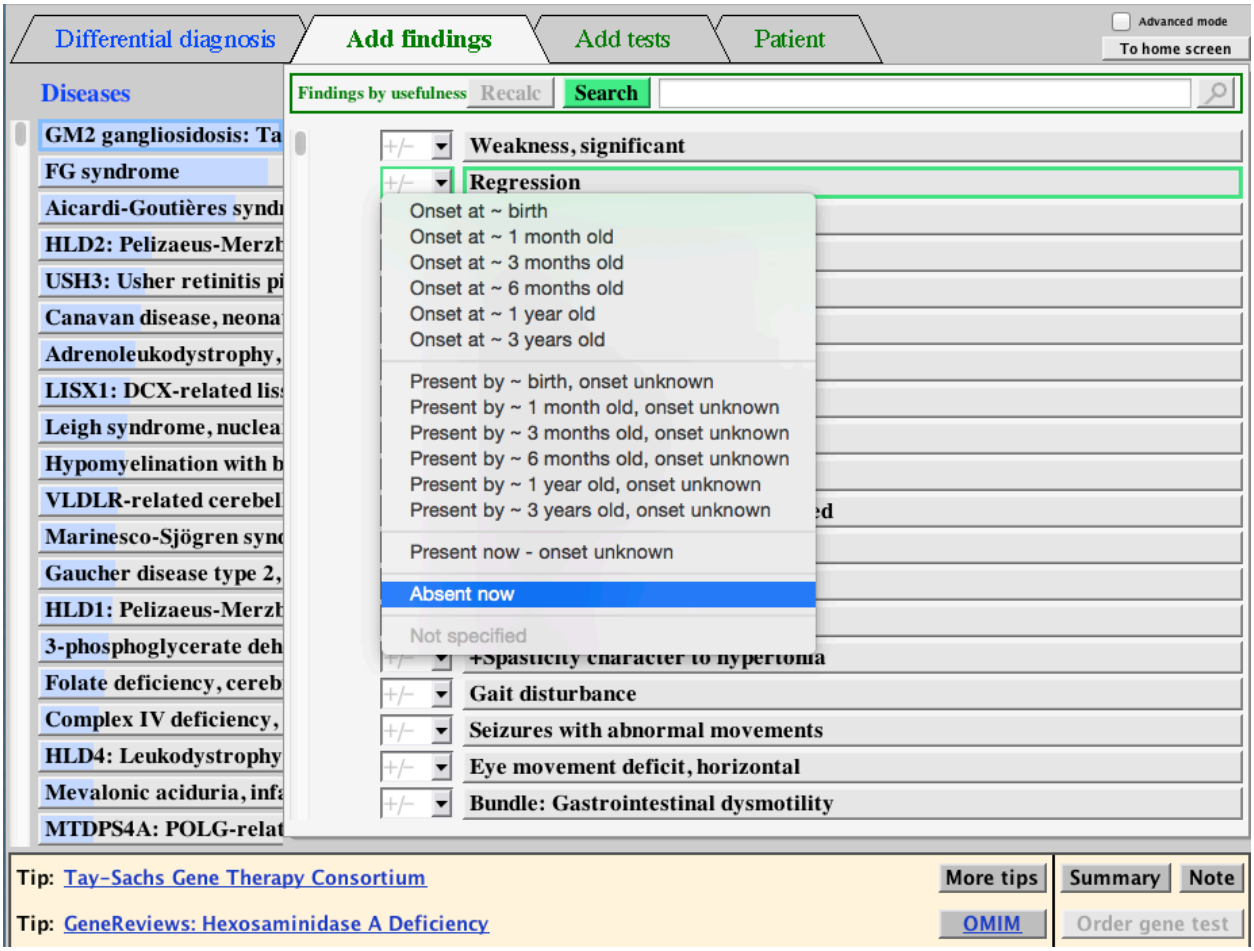
TIP

Notice the light blue shading representing the differential diagnosis overlay on the diseases.

Use suggested findings and tests

Click on the **Add findings** tab to get a suggestion of findings with which to narrow the differential diagnosis.

Figure 20: Entering findings using the 'Add (useful) findings' tab

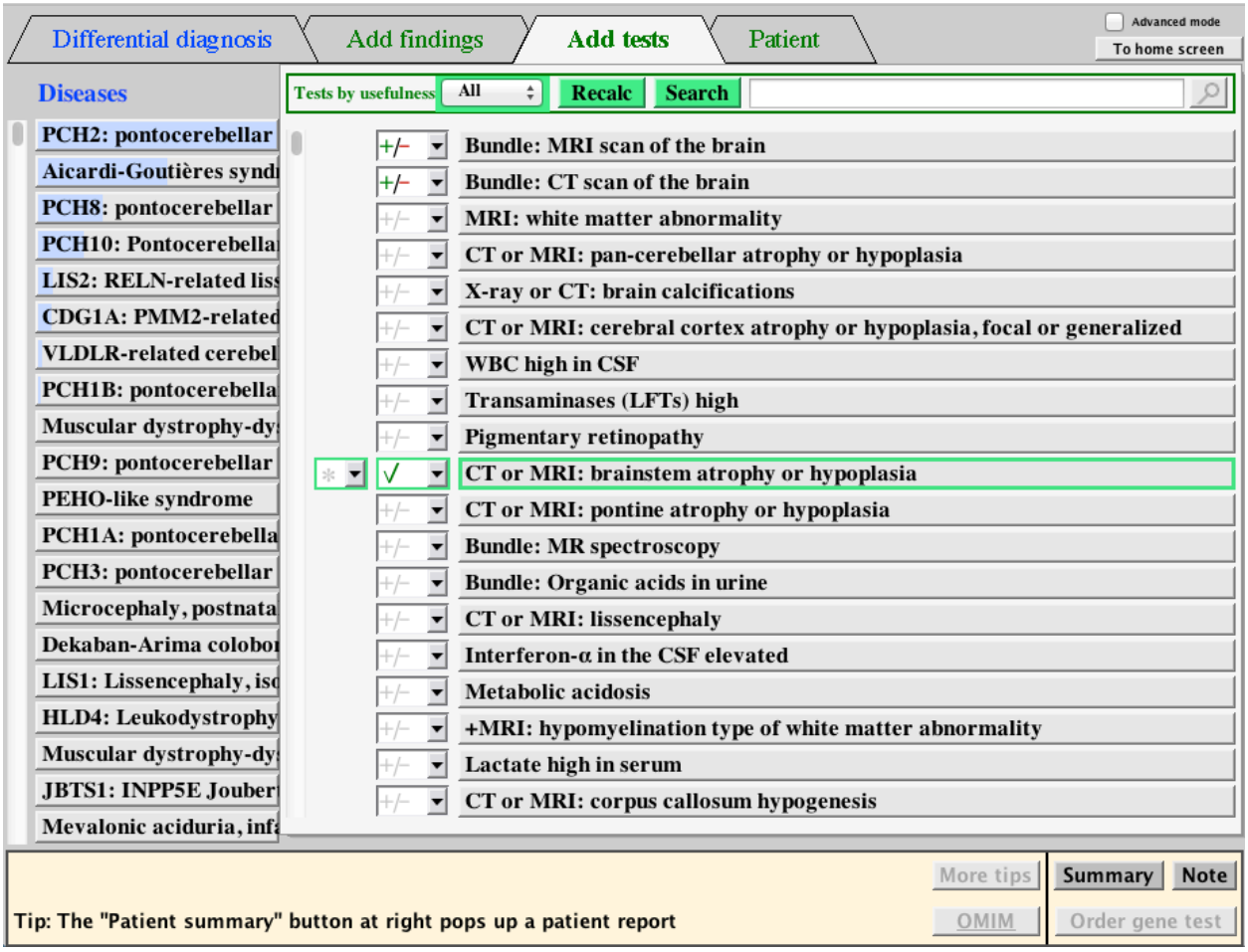


TIP

The differential diagnosis automatically recalculates every time a new finding is entered. By contrast, "**Add findings**" and "**Add tests**" recalculate manually. When you click the "**Recalc**" button, the commented findings move to the "**Patient**" tab.

Using the **Add tests**, we can comment on the results of the scan

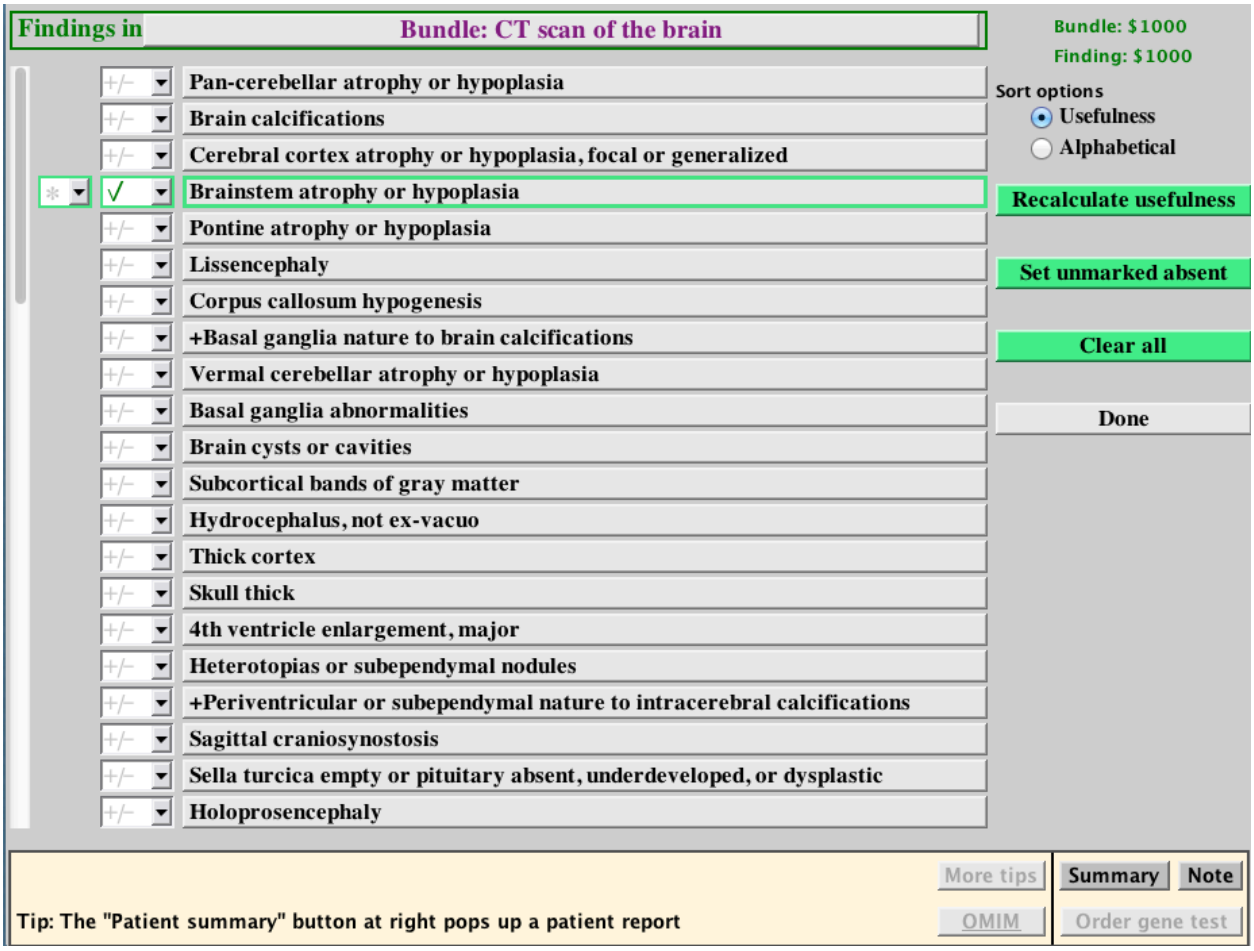
Figure 21: Entering findings using the 'Add (useful) tests' tab



Use test “bundles”, to find relevant value for tests with multiple outputs

Here we re-enter the finding of “CT or MRI: brainstem atrophy or hypoplasia” to show that there are multiple ways to navigate to the same finding.

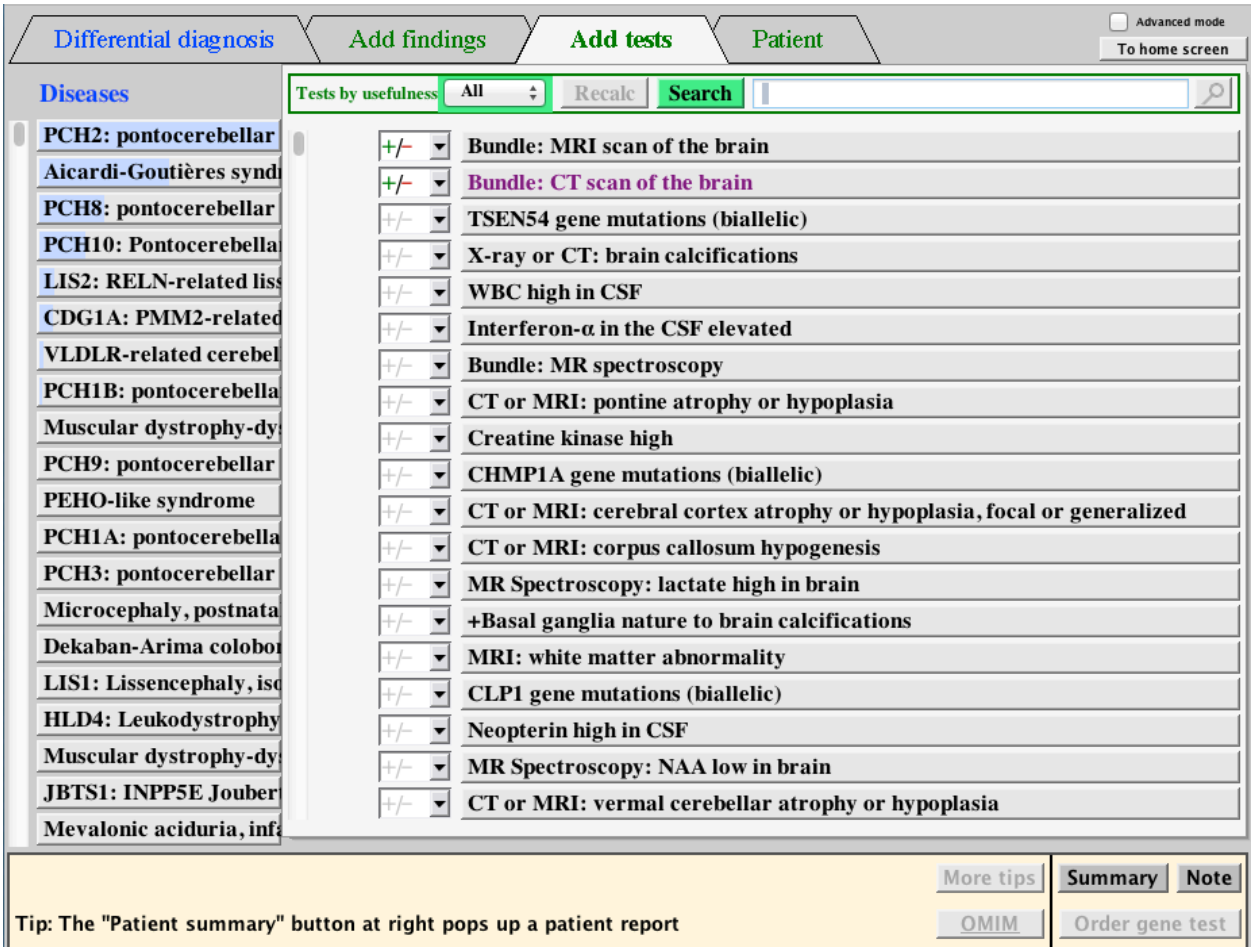
Figure 22: Entering test results using the ‘Bundles’ feature



Get back to the “QuickLists” and other search modes

To return to QuickLists or any of the other methods typically used for entering initial findings, click the green “**Search modes**” button.

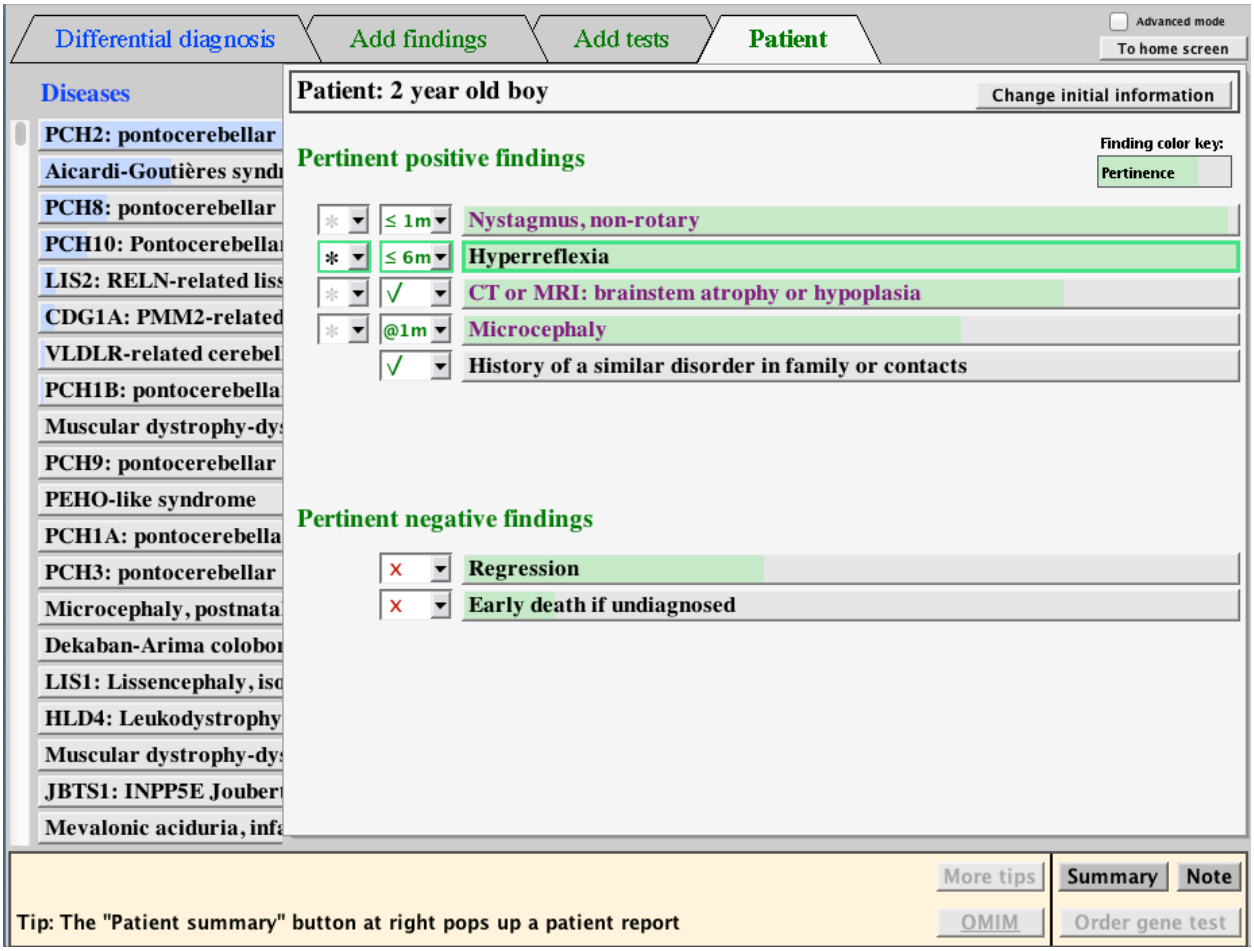
Figure 23: Getting back to the QuickLists



Require a finding

One or more findings may be so striking or unusual that you only want to see diseases with that finding. By default, the software includes the possibility a finding may be incidental. To override this default, 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 hyperreflexia. This is most useful for a common finding that is very striking in a patient.

Figure 24: How to require a finding



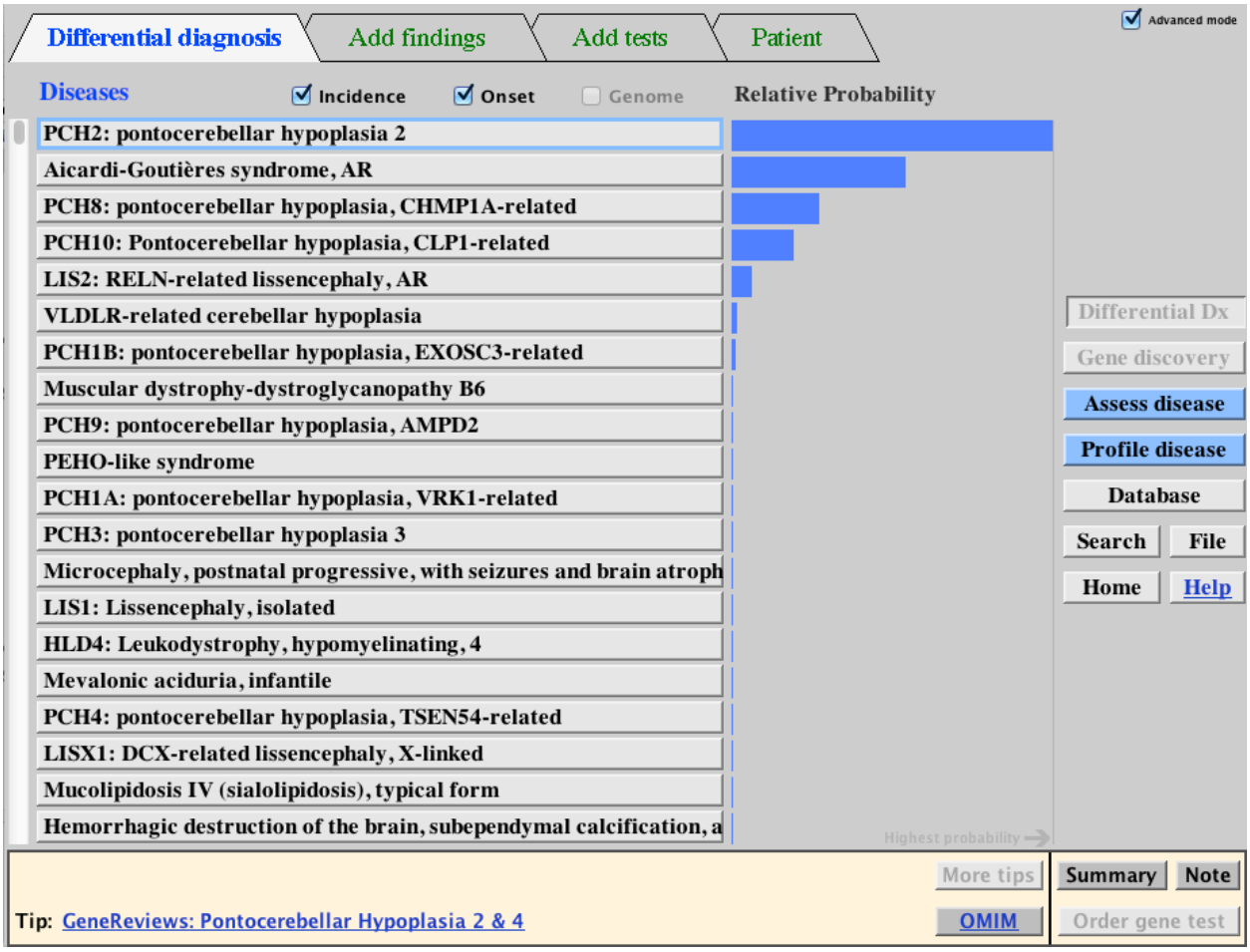
Advanced Mode: Use the "Profile disease"

To use this feature, click the "**Advanced**" button in the top right of your screen, then click on a button for a particular disease, then click the Profile disease button to view or comment on findings in that disease, including adding a set of pertinent negatives.

TIP

Use the disease profile when you suspect a disease.

Figure 25: Using Advanced mode and the disease profile



In addition to using the "**Profile disease**" screen as another vehicle to enter the same findings, the screen can be used to understand how a disease unfolds over time. Use the purple "**Scroll age**" button at the top right to see which findings will be present now (black), at each age, and also, how frequently overall that finding is present in that disease, but will emerge later (purple).

Figure 26: Entering findings using the 'Disease profile' list (shown at the patient's current age)

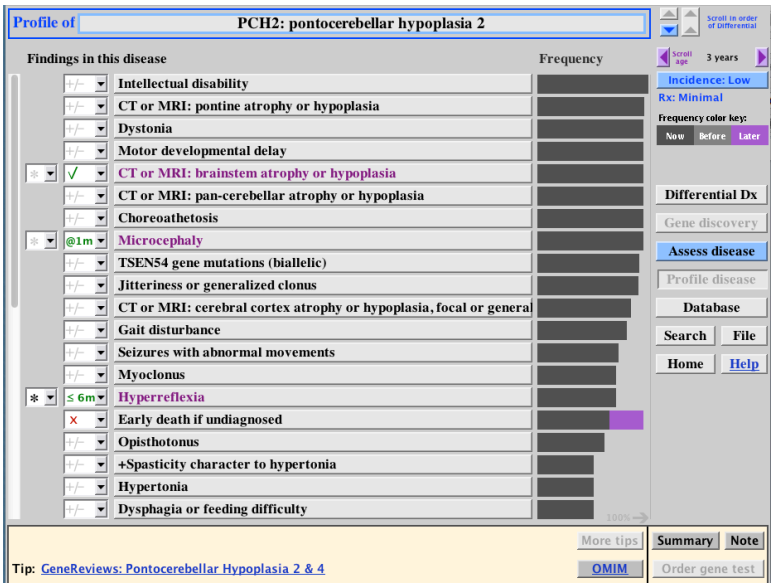
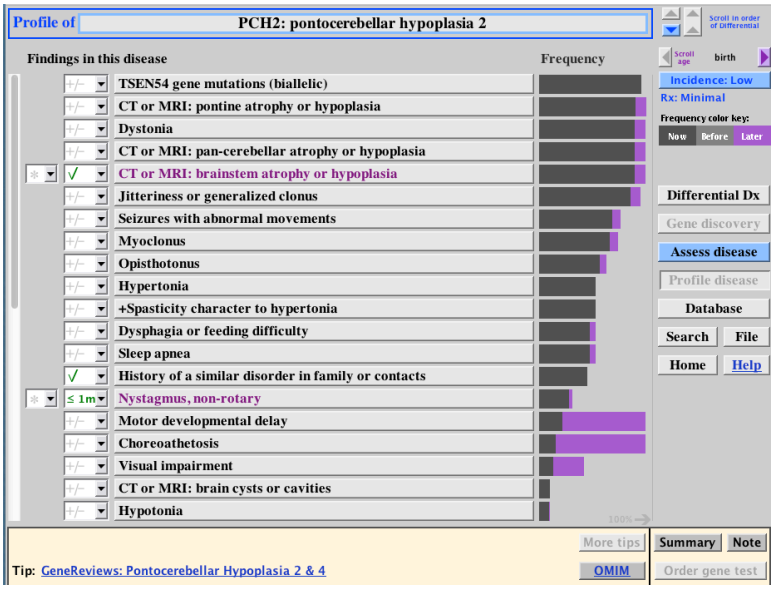


Figure 27: The same 'Disease Profile' for PCH2 shown at birth



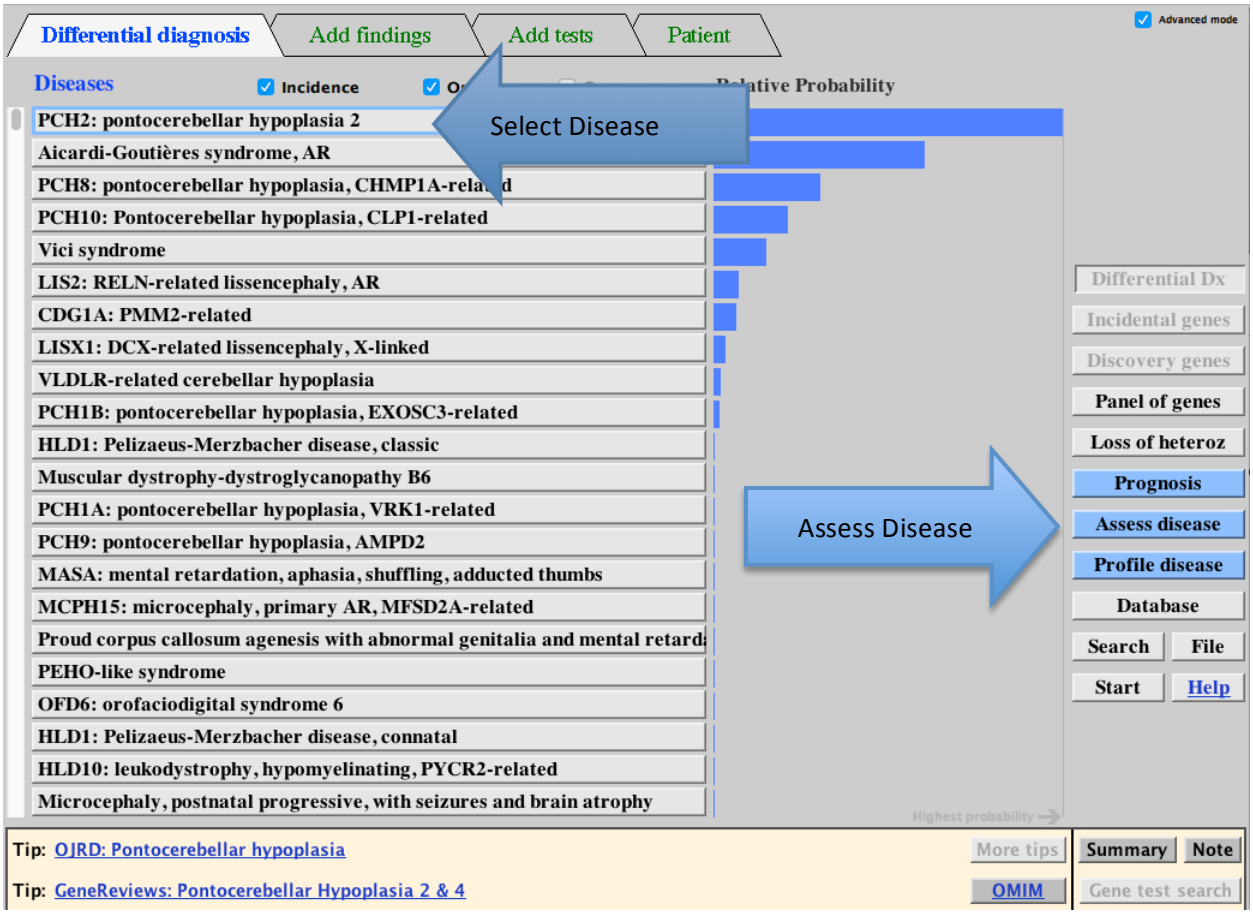
Advanced Mode: Use the "Assess disease"

When dictating a note about the rationale for the diagnosis, click on the top diseases in the differential diagnosis and select the **Assess Disease** button.

Figure 28: The Differential Diagnosis

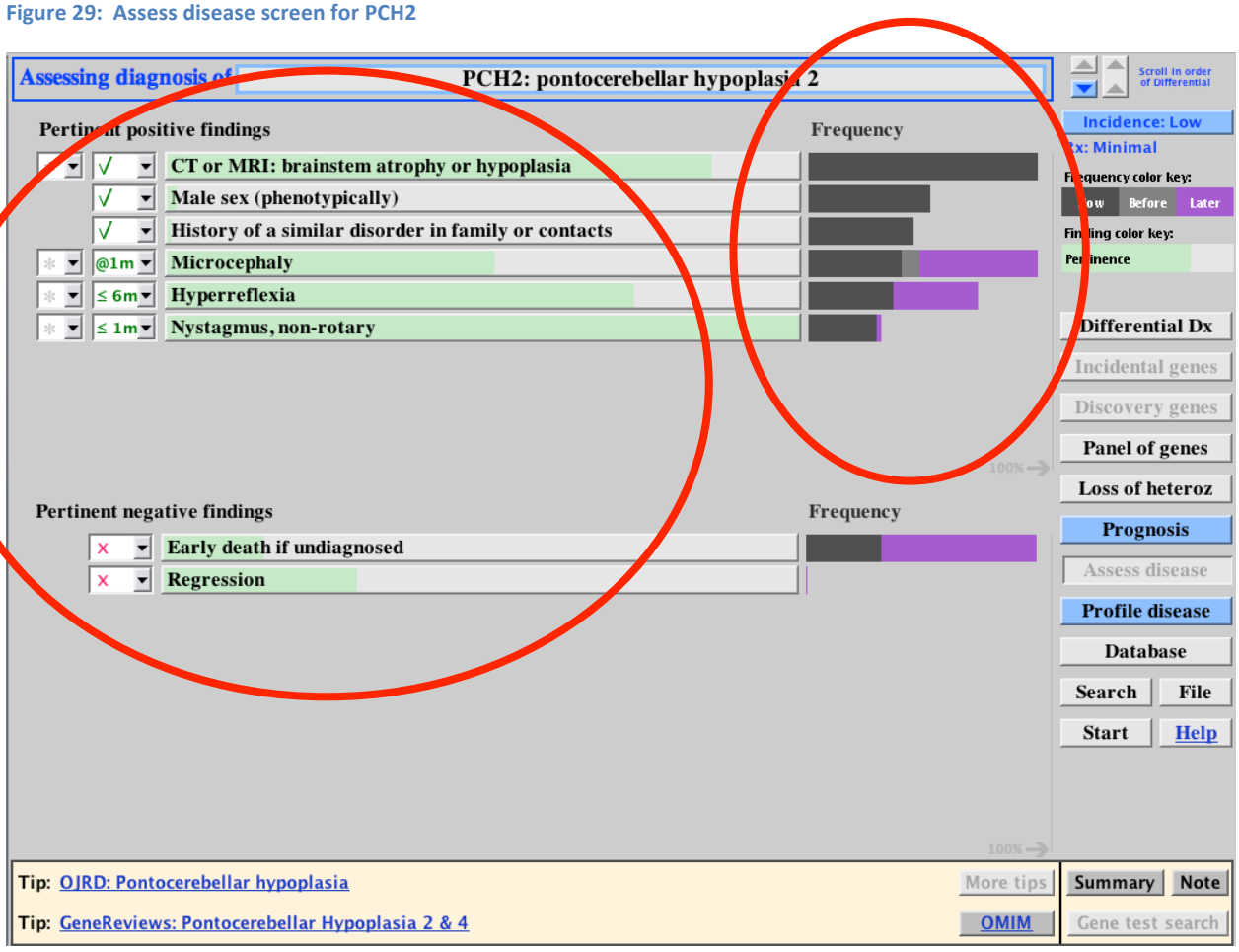
TIP

Use the Assess Disease when dictating your note to explain the rationale for your differential diagnosis.



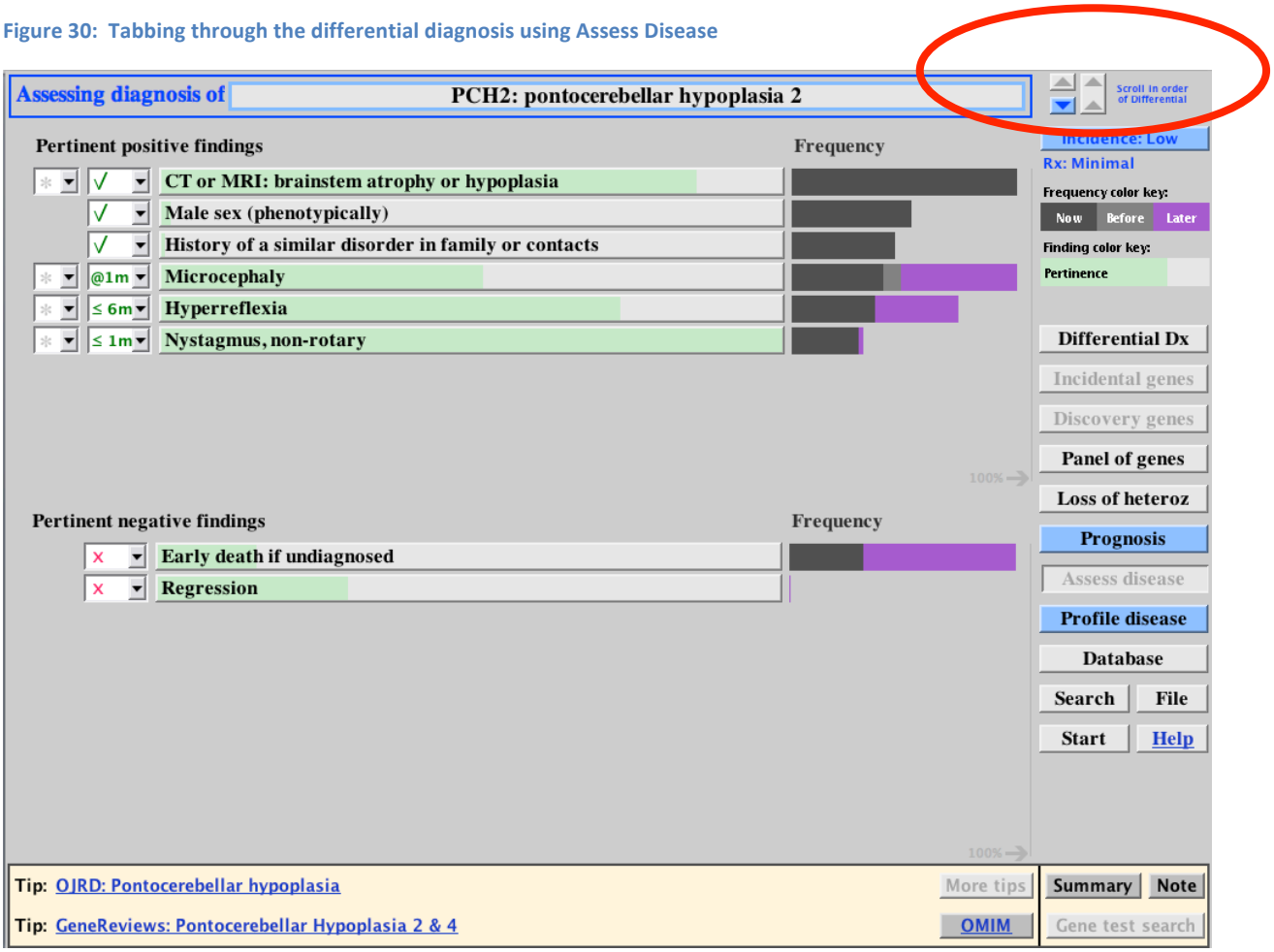
You will see a screen that super-imposes the patient findings on the frequency of those findings in the disease, in this case PCH2. The length of the frequency bar is the overall frequency of that finding in patients with PCH2. The color of the bar indicates the onset. Black for onset now, versus, onset at an earlier age in gray or later in purple.

Figure 29: Assess disease screen for PCH2



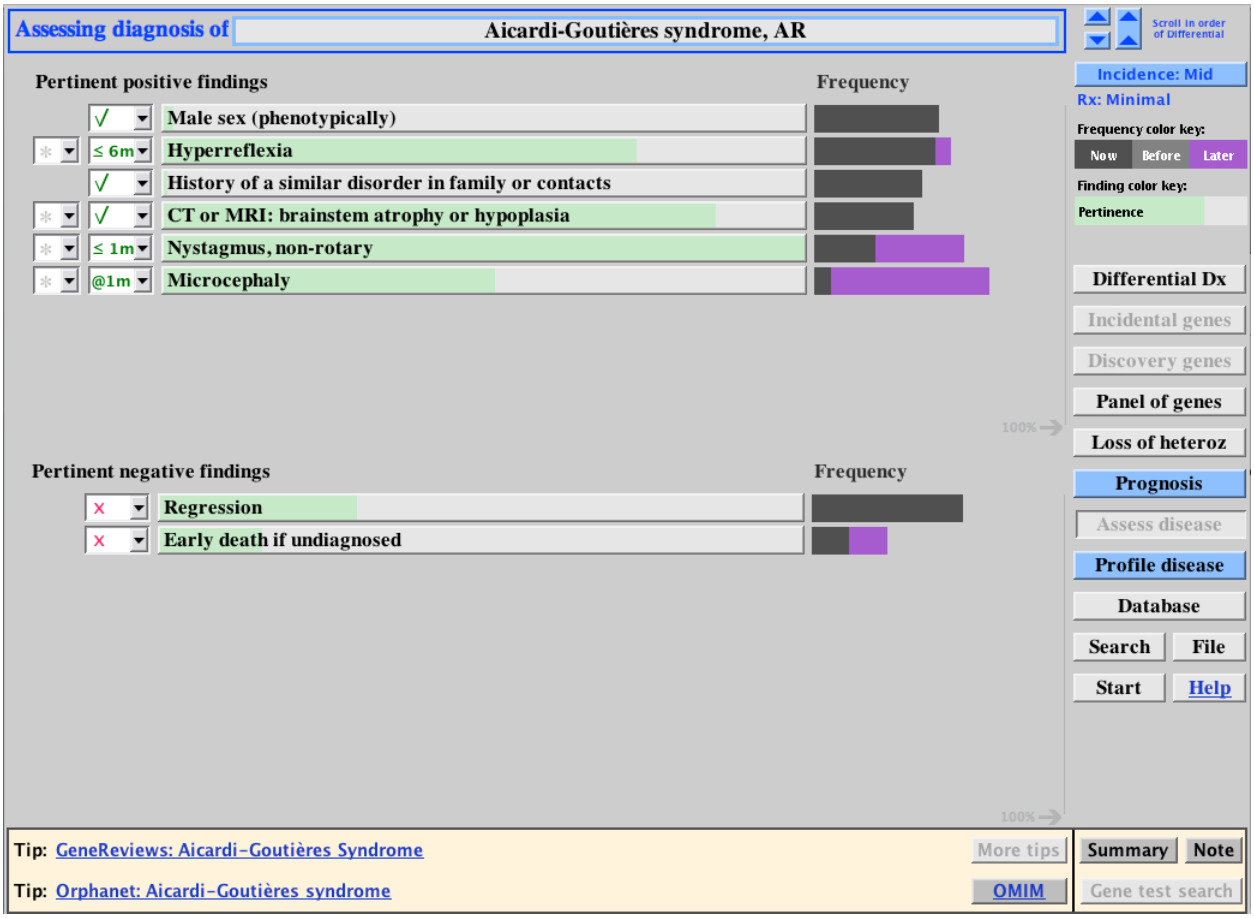
In general, a “good” fit is a lot of black on top and very little on the bottom. To see why Aicardi Goutieres syndrome is a less good fit, use the down arrow at the page to tab through the differential diagnosis diseases to see the fit.

Figure 30: Tabbing through the differential diagnosis using Assess Disease



Notice that in Aicardi-Goutieres syndrome roughly 60% of patients would have regression and all would have it by now, and in addition, perhaps 10% of patients would already have died. This makes it somewhat less likely that Aicardi-Goutieres is the diagnosis, as reflected in the differential diagnosis.

Figure 31: Fit of the #2 disease in Diff Dx

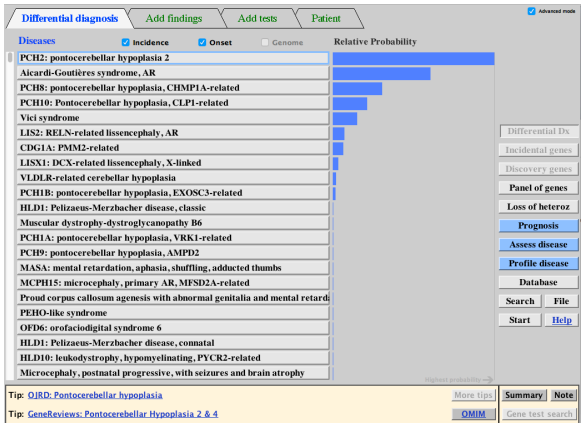


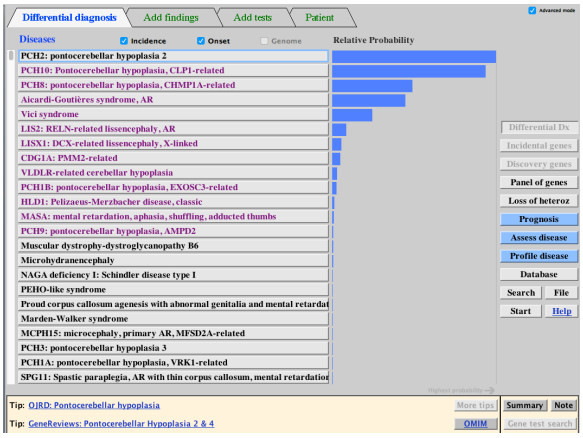
“Assess disease” and the importance of onset information

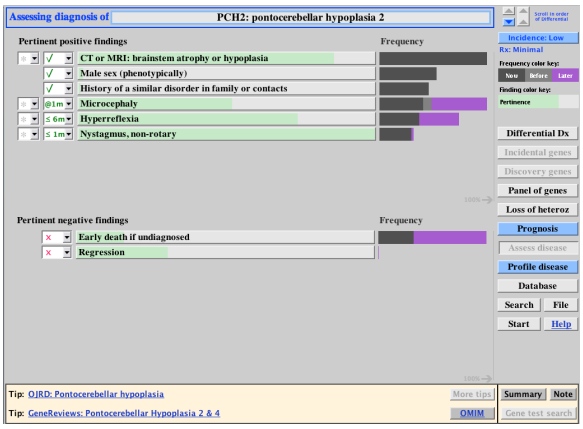
A simplistic notion of diagnosis simply specifies presence or absence, but this significantly reduces the ability to differentiate among diseases in the differential diagnosis. This is also obvious when looking at the Assess Disease, where the top diseases all seem like good fits.

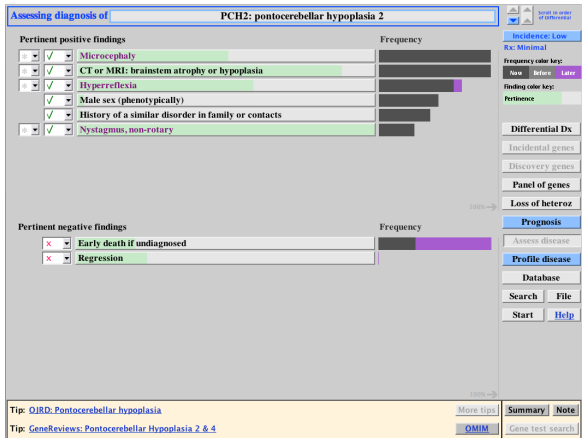
Not using onset leaves a less tight differential and makes the diseases seem equally probable. (Left is with onset, right is without.)

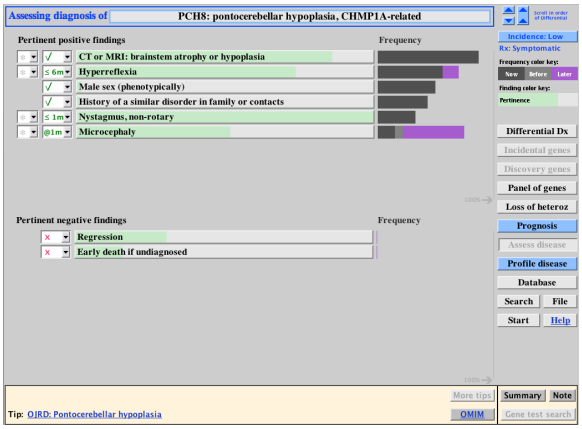
Figure 32: Differential and Assessment with and without onset

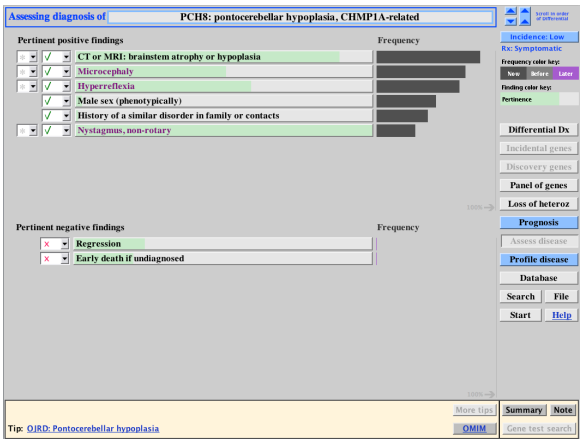












SAVE AND REOPEN PATIENT HISTORY

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. **Query string:** SimulConsult has created special codes (in the form of a query 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 query 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 query string that can be saved. Note: since only medical professionals may have direct access to SimulConsult it is not advised to put the query string in the note, if notes are open to patient inspection, such as through Open Notes.

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

Save the “Summary” with the “Finding Code”

There are two ways to save the patient findings, depending on your purpose.

1. Click on the “**Summary**” button and then save the HTML page using the save command in your browser. Note: this produces a version that is both human readable and also can be reopened and read by the software.

Figure 33: Generating the HTML Patient Summary

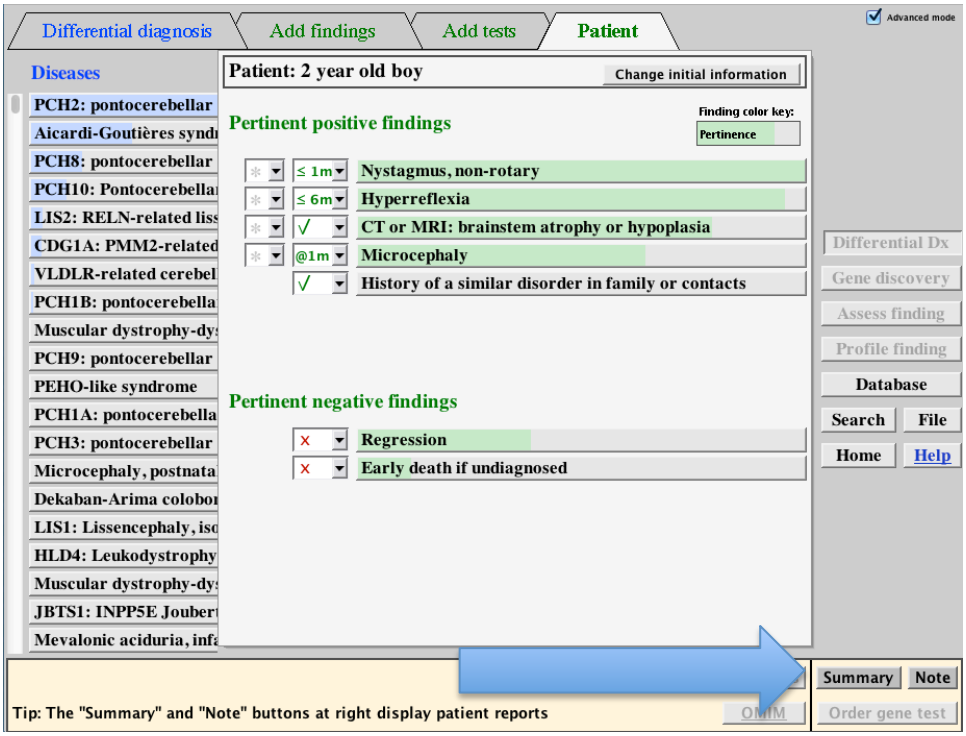
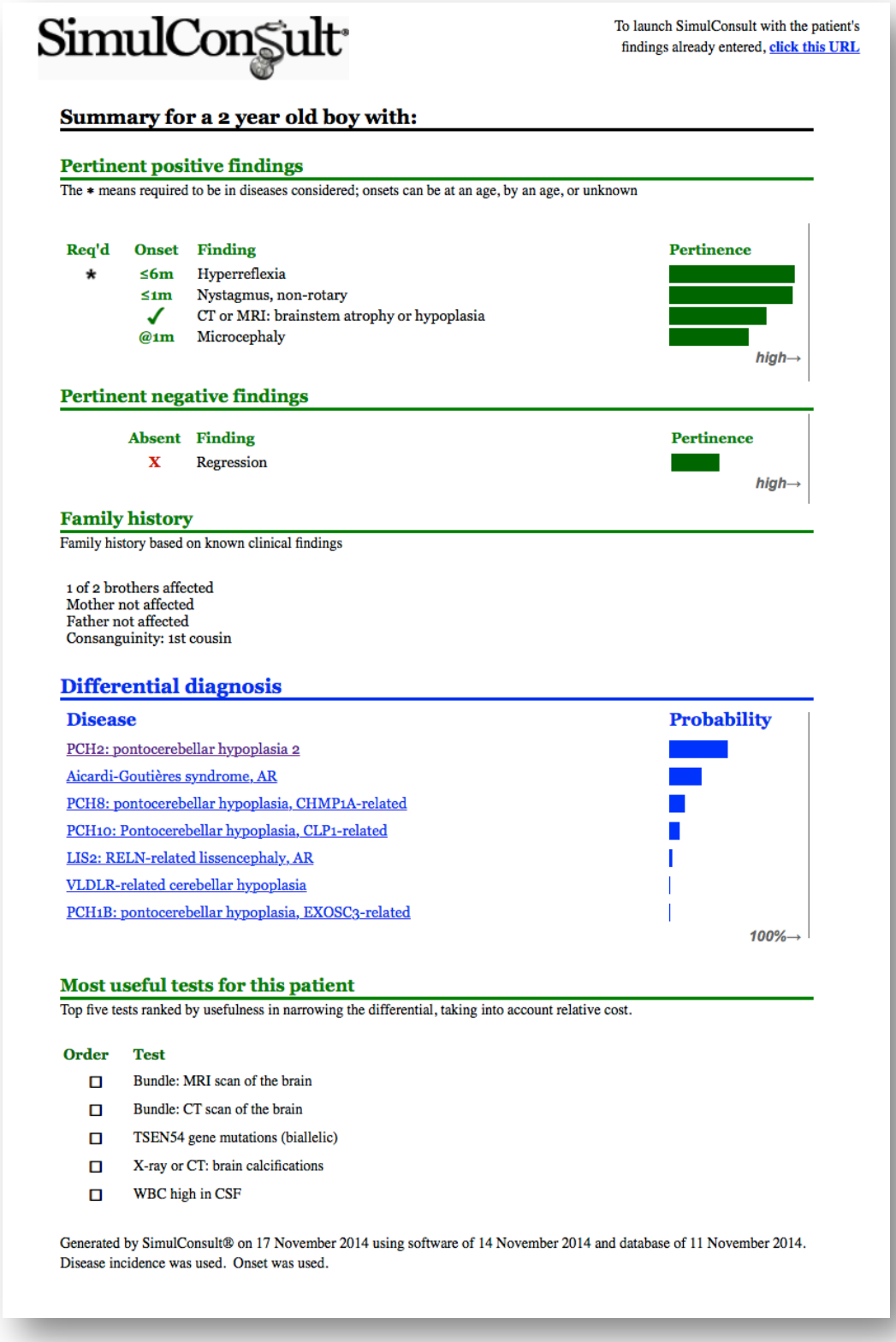


Figure 34: The HTML Patient Summary (can be saved, printed, or printed to PDF)



SimulConsult®

To launch SimulConsult with the patient's findings already entered, click this URL

Summary for a 2 year old boy with:

Pertinent positive findings

The * means required to be in diseases considered; onsets can be at an age, by an age, or unknown

Req'd	Onset	Finding	Pertinence
*	≤6m	Hyperreflexia	
	≤1m	Nystagmus, non-rotary	
	✓	CT or MRI: brainstem atrophy or hypoplasia	
	@1m	Microcephaly	

high→

Pertinent negative findings

Absent	Finding	Pertinence
X	Regression	

high→

Family history

Family history based on known clinical findings

1 of 2 brothers affected
Mother not affected
Father not affected
Consanguinity: 1st cousin

Differential diagnosis

Disease	Probability
PCH2: pontocerebellar hypoplasia 2	
Aicardi-Goutières syndrome, AR	
PCH8: pontocerebellar hypoplasia, CHMP1A-related	
PCH10: Pontocerebellar hypoplasia, CLP1-related	
LIS2: RELN-related lissencephaly, AR	
VLDLR-related cerebellar hypoplasia	
PCH1B: pontocerebellar hypoplasia, EXOSC3-related	

100%→

Most useful tests for this patient

Top five tests ranked by usefulness in narrowing the differential, taking into account relative cost.

Order	Test
☐	Bundle: MRI scan of the brain
☐	Bundle: CT scan of the brain
☐	TSEN54 gene mutations (biallelic)
☐	X-ray or CT: brain calcifications
☐	WBC high in CSF

Generated by SimulConsult® on 17 November 2014 using software of 14 November 2014 and database of 11 November 2014.
Disease incidence was used. Onset was used.

2. The second approach to saving the patient information uses the "**File**" button visible in the **advanced mode**.

Figure 35: Save the Patient Summary using the advanced mode and file button

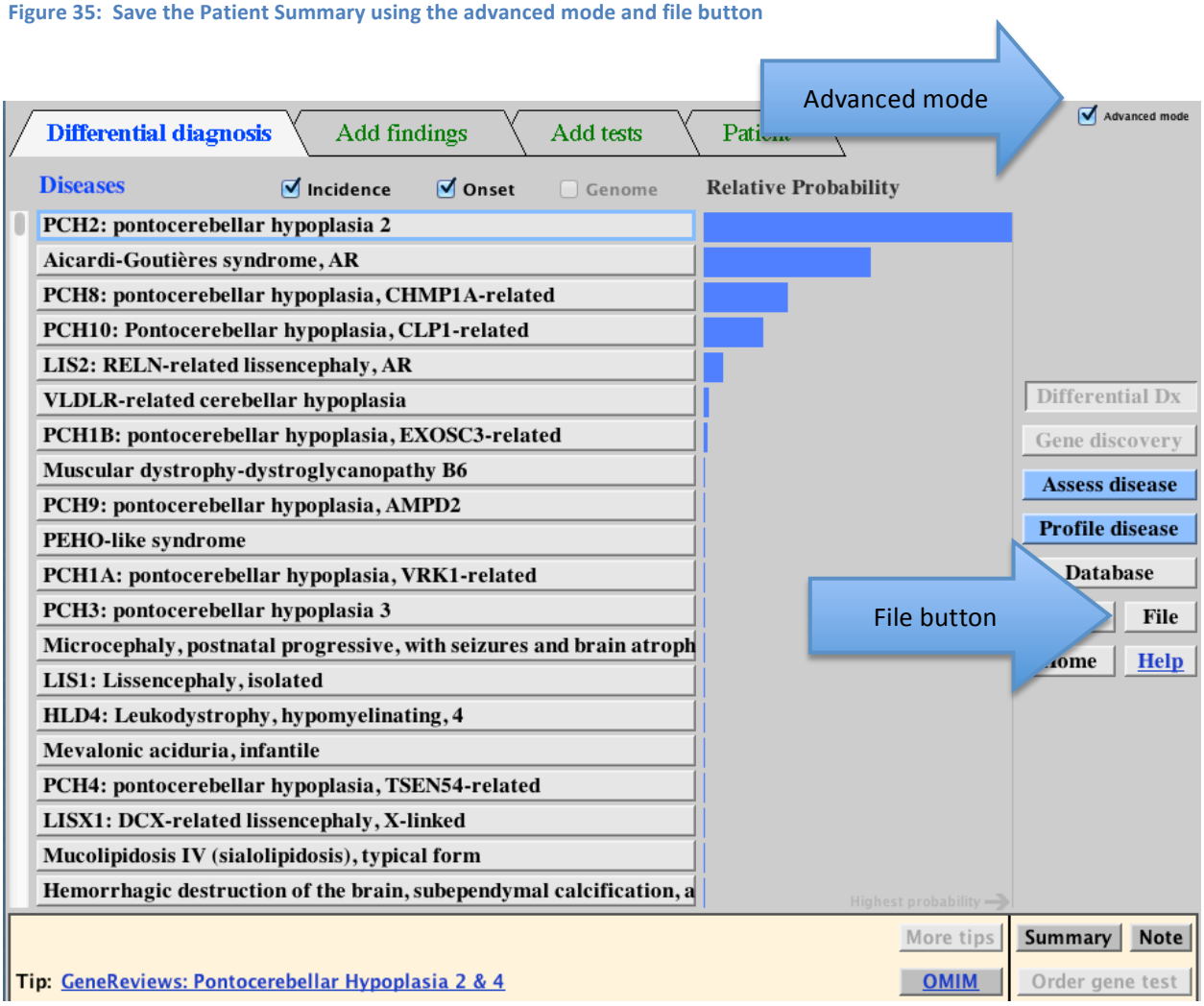
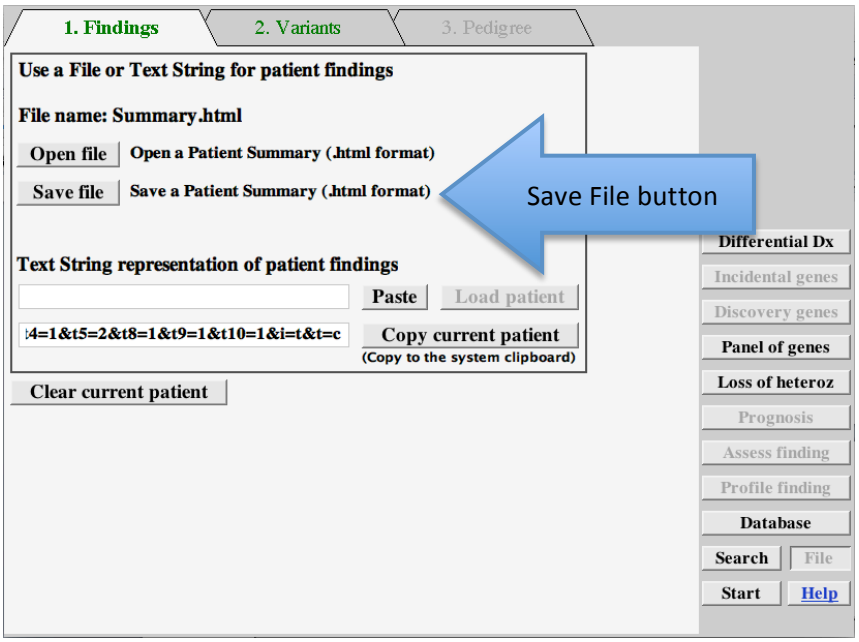


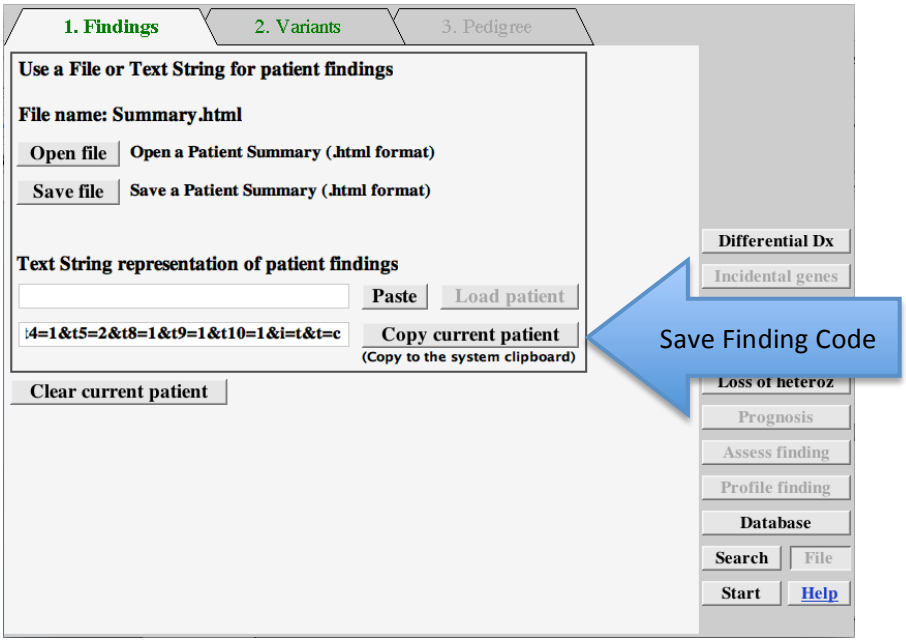
Figure 36: Saving the Patient Summary



Save the "Finding Code" directly

You can also choose to save the find code, which will allow you to reopen the patient. This is often useful in a shared exam room where you can not save to the desktop. Use the copy current patient button and paste the code in an email to yourself.

Figure 37: Save the finding code directly



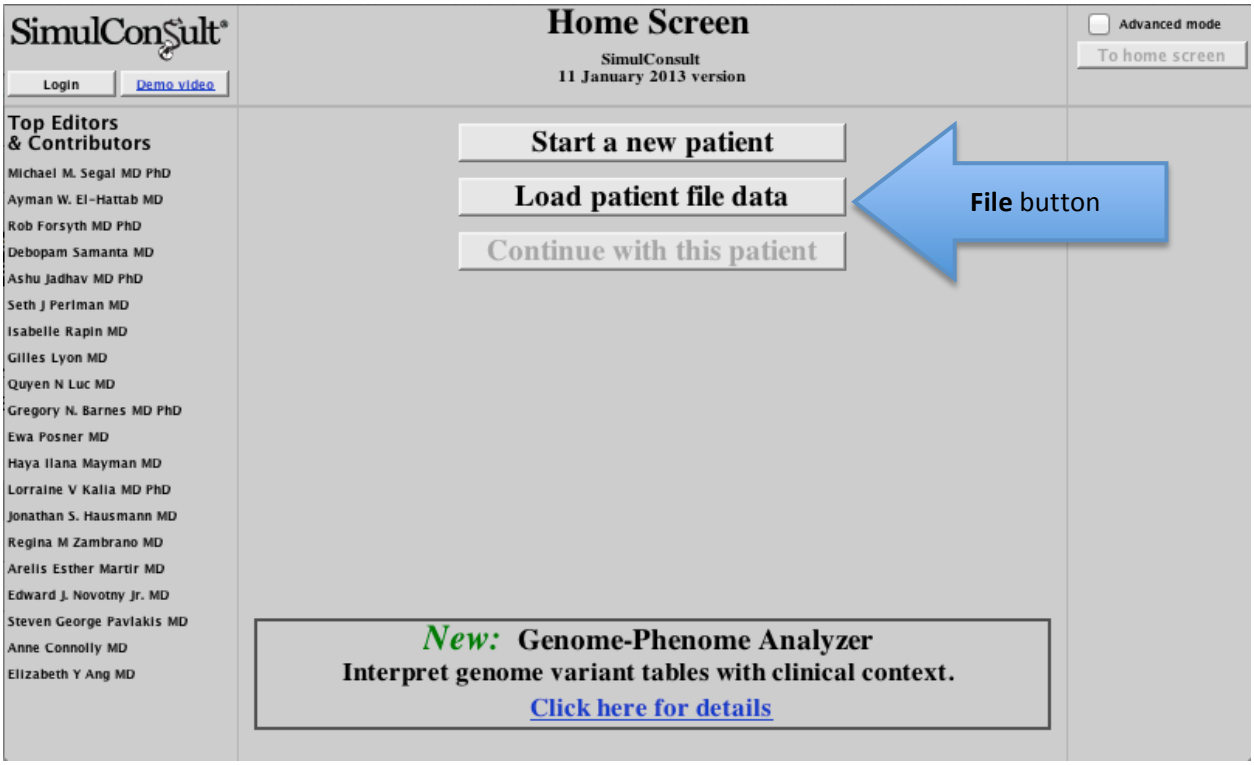
Open previously saved findings

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. In **advanced mode**, use the "**File**" button for to open the previously saved file. If you have an enterprise version, use the links described in the companion guide for launching and saving in your environment.

Note: those with Genome-Phenome privileges also can save a step and load a previously saved patient file from the Home screen.

Figure 38: Load patient data



Note: For those with Genome-Phenome privileges, you must enter clinical findings directly or open a previously saved patient file of clinical findings before you can open a variant table.

Figure 39: Open patient file

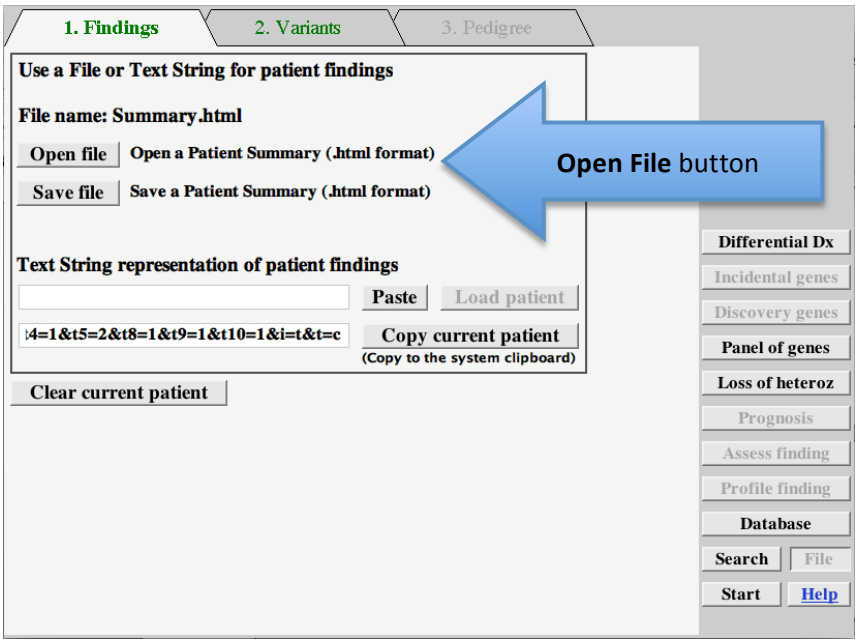
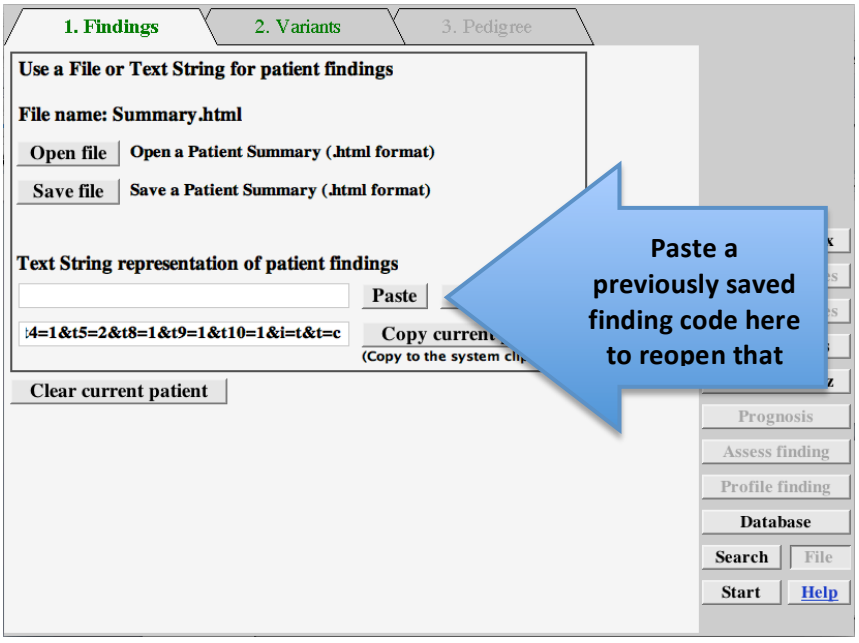


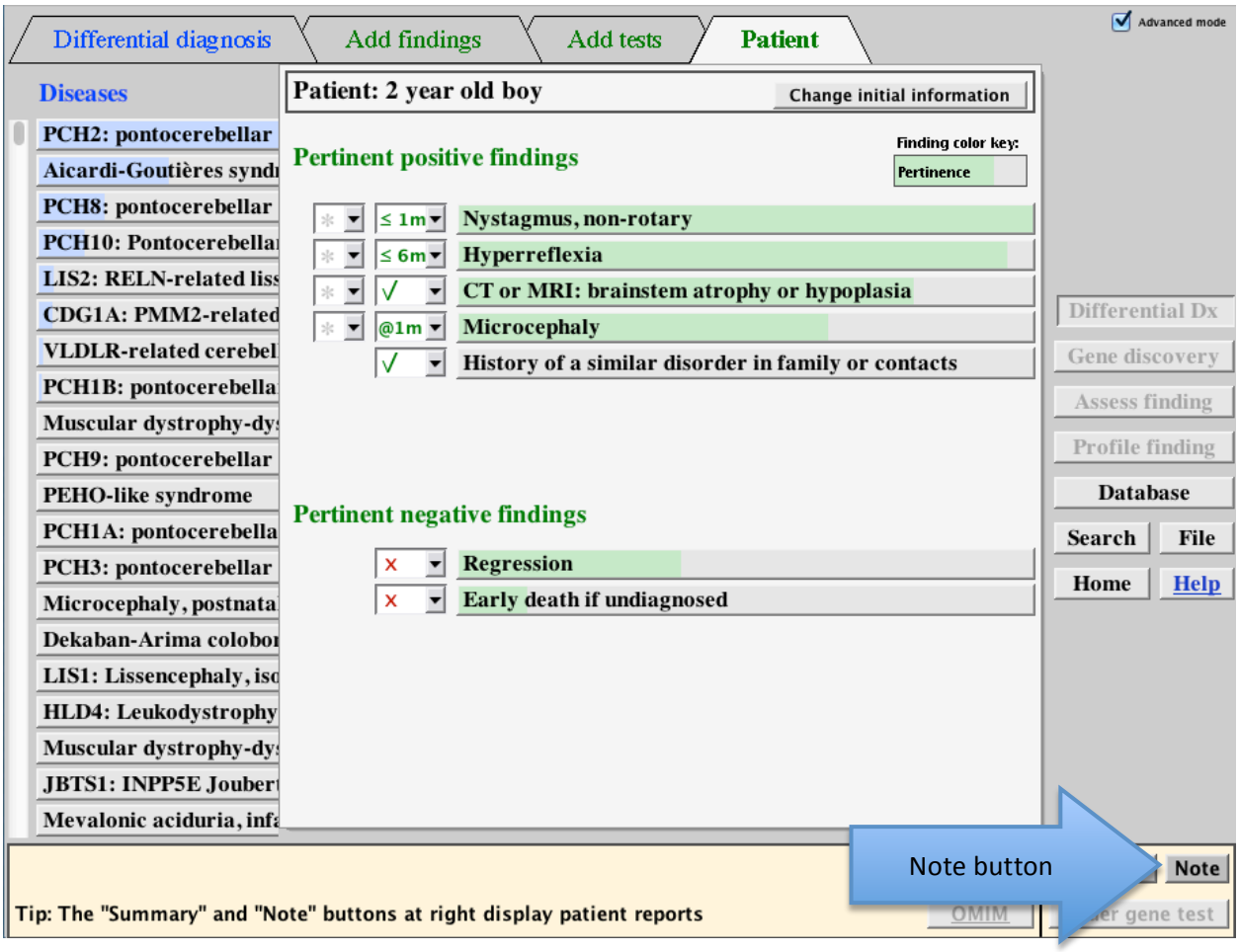
Figure 40: Open using the Finding Code



Saving the “Note”

The Note can be saved using the Note button.

Figure 41: Note button



The output of the Note is organized into traditional groups. In some implementations, it outputs as a single unit of text. In others, it has been broken into sections and can be placed within an existing note template.

Figure 42: SOAP Note output in plain text

HISTORY OF PRESENT ILLNESS

This is a 2 year old boy with
Nystagmus, non-rotary, onset by 1 month old
Microcephaly, onset at 1 month old
Hyperreflexia, onset by 6 months old
CT or MRI: brainstem atrophy or hypoplasia, present now

Regression, absent

Growth / development

Microcephaly, onset at 1 month old

FAMILY HISTORY

1 of 2 brothers affected
Mother not affected
Father not affected
Consanguinity: 1st cousin

PHYSICAL EXAM

Present
Hyperreflexia
Nystagmus, non-rotary
Microcephaly

LAB / STUDIES

Present
CT or MRI: brainstem atrophy or hypoplasia, present now

ASSESSMENT

This is a 2 year old boy with:

Pertinent positives

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

Pertinent negatives

Regression

Differential Diagnosis

PCH2: pontocerebellar hypoplasia 2
Aicardi-Goutieres syndrome, AR
PCH8: pontocerebellar hypoplasia, CHMP1A-related
PCH10: Pontocerebellar hypoplasia, CLP1-related
LIS2: RELN-related lissencephaly, AR
VLDLR-related cerebellar hypoplasia
PCH1B: pontocerebellar hypoplasia, EXOSC3-related

PLAN

Most useful tests for this patient

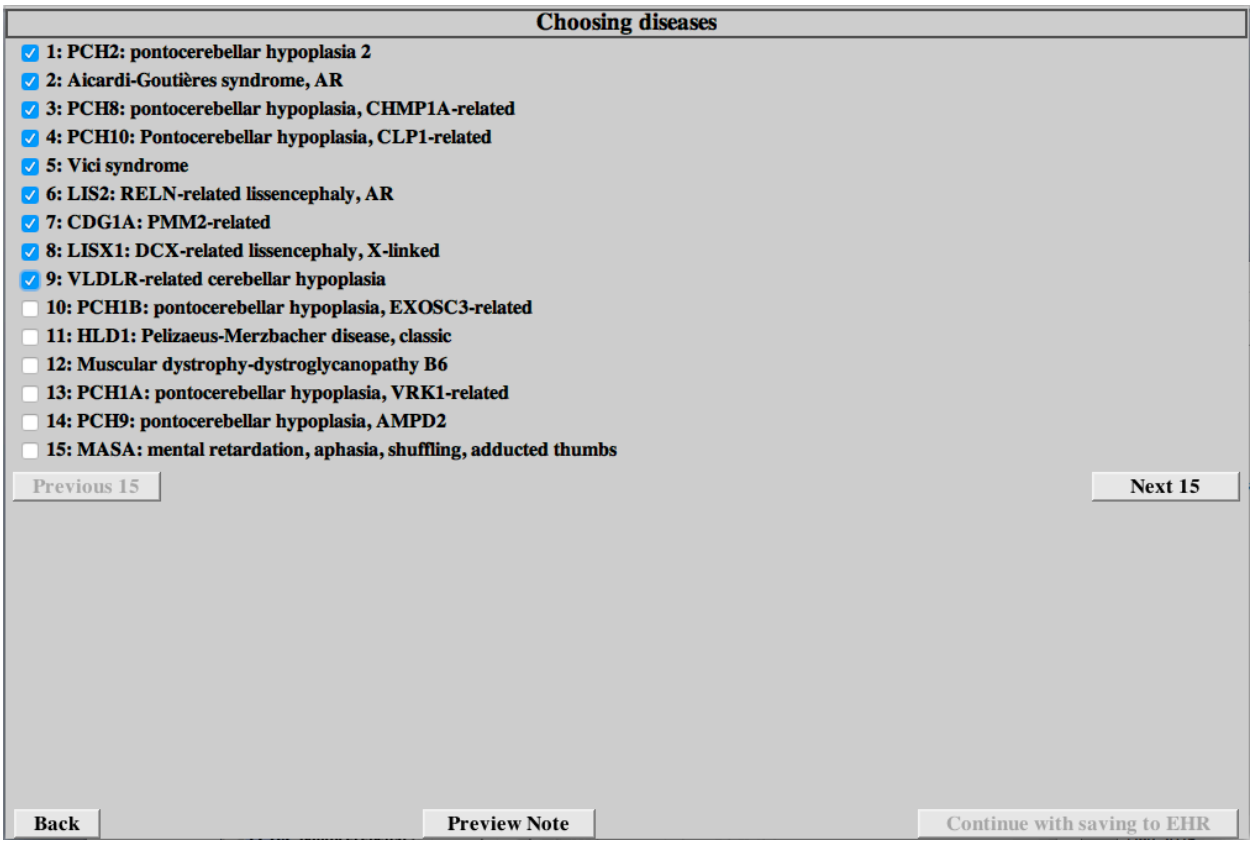
Bundle: MRI scan of the brain
Bundle: CT scan of the brain
TSEN54 gene mutations (biallelic)
X-ray or CT: brain calcifications
WBC high in CSF

Some of this data was entered using the Simulconsult Diagnostic Decision Support software. To re-launch the software with the patient's findings as used in this session, copy and paste this URL into a browser window:

http://www.simulconsult.com/run/?d=730&u=ftemp1&o=499999&u=ftemp20&o=59&u=ftemp158&o=399999&u=ftemp220&o=b59&u=ftemp270&o=rb269&u=segal_020614172829&o=

You have the option to select the diseases you want to include in the differential diagnosis before viewing the note.

Figure 43: Select diseases to include in Note before generating Note



If you select a subset of the diseases, the note reflects it.

Figure 44: Note with subset of selected diagnoses in Diff Dx

HISTORY OF PRESENT ILLNESS

This is a 2 year old boy with
Nystagmus, non-rotary, onset by about 1 month old
Microcephaly, onset at about 1 month old
Hyperreflexia, onset by about 6 months old
CT or MRI: brainstem atrophy or hypoplasia, present now

Regression, absent

Growth / development

Microcephaly, onset at about 1 month old

FAMILY HISTORY

1 of 2 brothers affected
Mother not affected
Father not affected
Consanguinity: 1st cousin

PHYSICAL EXAM

Present
Nystagmus, non-rotary
Hyperreflexia
Microcephaly

LAB / STUDIES

Present
CT or MRI: brainstem atrophy or hypoplasia, present now

ASSESSMENT

This is a 2 year old boy with:

Pertinent positives

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

Pertinent negatives

Regression

Differential Diagnosis

PCH2: pontocerebellar hypoplasia 2
Aicardi-Goutieres syndrome, AR
PCH8: pontocerebellar hypoplasia, CHMP1A-related
PCH10: Pontocerebellar hypoplasia, CLP1-related
Vici syndrome
LIS2: RELN-related lissencephaly, AR
CDG1A: PMM2-related
LISX1: DCX-related lissencephaly, X-linked
VLDLR-related cerebellar hypoplasia

PLAN

Most useful tests for this patient

Bundle: MRI scan of the brain
Bundle: CT scan of the brain
Personalized panel: 13 most useful genes
X-ray or CT: brain calcifications
TSEN54 gene mutations (biallelic)

Finally, if you have a relationship with Intelligent Medical Objects, we can enable automatic coding of the diseases using ICD10.

PREMIUM UPGRADE OPTIONS: THE PROGNOSIS TABLE

SimulConsult currently offers an upgrade option to the Phenome version to have access to the Prognosis Table for all 6,000-plus diseases. When returning results and a diagnosis to patients and their primary care physicians, it is often helpful to have an intuitive way to convey the expectations about how the disease will unfold. Research has shown the Prognosis table needs no explanation.

Figure 45: Prognosis Table

Prognosis for PCH2: pontocerebellar hypoplasia 2

	At what age do people with this disease have these findings?												
Signs and Symptoms	**Birth**	**1 month**	**3 months**	**6 months**	**1 year**	**3 years**	**6 years**	**10 years**	**15 years**	**25 years**	**40 years**	**60 years**	**80 years**
Dystonia	Most	Most	Most	Most	Most	Most	Most	Most	Most	Most	Most	Most	Most
Jitteriness or generalized clonus	Some	Most	Most	Most	Most	Most	Most	Most	Most	Most	Most	Most	Most
Microcephaly	Few	Some	Most	Most	Most	Most	Most	Most	Most	Most	Most	Most	Most
Choreoathetosis	Few	Some	Some	Most	Most	Most	Most	Most	Most	Most	Most	Most	Most
Motor developmental delay	Few	Some	Some	Most	Most	Most	Most	Most	Most	Most	Most	Most	Most
Intellectual disability	NA	Few	Few	Some	Most	Most	Most	Most	Most	Most	Most	Most	Most
Spasticity character to hypertonia	Some	Some	Some	Some	Some	Some	Some	Some	Some	Some	Some	Some	Some
Myoclonus	Some	Some	Some	Some	Some	Some	Some	Some	Some	Some	Some	Some	Some
Opisthotonus	Some	Some	Some	Some	Some	Some	Some	Some	Some	Some	Some	Some	Some
Hypertonia / stiffness	Some	Some	Some	Some	Some	Some	Some	Some	Some	Some	Some	Some	Some
Sleep apnea	Some	Some	Some	Some	Some	Some	Some	Some	Some	Some	Some	Some	Some
Seizures with abnormal movements	Some	Some	Some	Some	Some	Some	Some	Some	Some	Some	Some	Some	Some
Dysphagia or feeding difficulty	Some	Some	Some	Some	Some	Some	Some	Some	Some	Some	Some	Some	Some
Nystagmus, non-rotary	Few	Few	Some	Some	Some	Some	Some	Some	Some	Some	Some	Some	Some
Visual impairment despite lens correction	Few	Few	Some	Some	Some	Some	Some	Some	Some	Some	Some	Some	Some
Hyperreflexia	NA	Few	Few	Some	Some	Some	Some	Some	Some	Some	Some	Some	Some
Gait disturbance	NA	NA	NA	NA	Some	Some	Some	Some	Some	Some	Some	Some	Some
Contractures or passive limited range of motion	Few	Few	Few	Few	Few	Few	Few	Few	Few	Few	Few	Few	Few
Irritability or agitation, pronounced	Few	Few	Few	Few	Few	Few	Few	Few	Few	Few	Few	Few	Few
Stature short	Few	Few	Few	Few	Few	Few	Few	Few	Few	Few	Few	Few	Few
Heat, fever, or systemic infection triggers attacks or aggravates findings	Few	Few	Few	Few	Few	Few	Few	Few	Few	Few	Few	Few	Few
Ataxia	Few	Few	Few	Few	Few	Few	Few	Few	Few	Few	Few	Few	Few
Scoliosis with or without kyphosis	Few	Few	Few	Few	Few	Few	Few	Few	Few	Few	Few	Few	Few
Hypotonia	Few	Few	Few	Few	Few	Few	Few	Few	Few	Few	Few	Few	Few
Findings detected by laboratory tests													
CT or MRI: brainstem atrophy or hypoplasia	Most	Most	Most	Most	Most	Most	Most	Most	Most	Most	Most	Most	Most
CT or MRI: pontine atrophy or hypoplasia	Most	Most	Most	Most	Most	Most	Most	Most	Most	Most	Most	Most	Most
CT or MRI: pan-cerebellar atrophy or hypoplasia	Most	Most	Most	Most	Most	Most	Most	Most	Most	Most	Most	Most	Most
TSEN54 gene mutations (biallelic)	Most	Most	Most	Most	Most	Most	Most	Most	Most	Most	Most	Most	Most
Creatine kinase high	Few	Few	Few	Some	Some	Some	Some	Some	Some	Some	Some	Some	Some
CT or MRI: cerebral cortex atrophy or hypoplasia	NA	NA	Few	Some	Some	Some	Some	Some	Some	Some	Some	Some	Some
MRI: white matter abnormality	NA	NA	Few	Few	Few	Some	Some	Some	Some	Some	Some	Some	Some
Myoglobinuria	Few	Few	Few	Few	Few	Few	Few	Few	Some	Some	Some	Some	Some
CT or MRI: brain cysts or cavities	Few	Few	Few	Few	Few	Few	Few	Few	Few	Few	Few	Few	Few
X-ray: osteopenia	Few	Few	Few	Few	Few	Few	Few	Few	Few	Few	Few	Few	Few
Renal failure or severe dysfunction	Few	Few	Few	Few	Few	Few	Few	Few	Few	Few	Few	Few	Few
TSEN34 gene mutations (biallelic)	Few	Few	Few	Few	Few	Few	Few	Few	Few	Few	Few	Few	Few
TSEN2 gene mutations (biallelic)	Few	Few	Few	Few	Few	Few	Few	Few	Few	Few	Few	Few	Few
SEPSECS gene mutations (biallelic)	Few	Few	Few	Few	Few	Few	Few	Few	Few	Few	Few	Few	Few
VPS53 gene mutations (biallelic)	Few	Few	Few	Few	Few	Few	Few	Few	Few	Few	Few	Few	Few

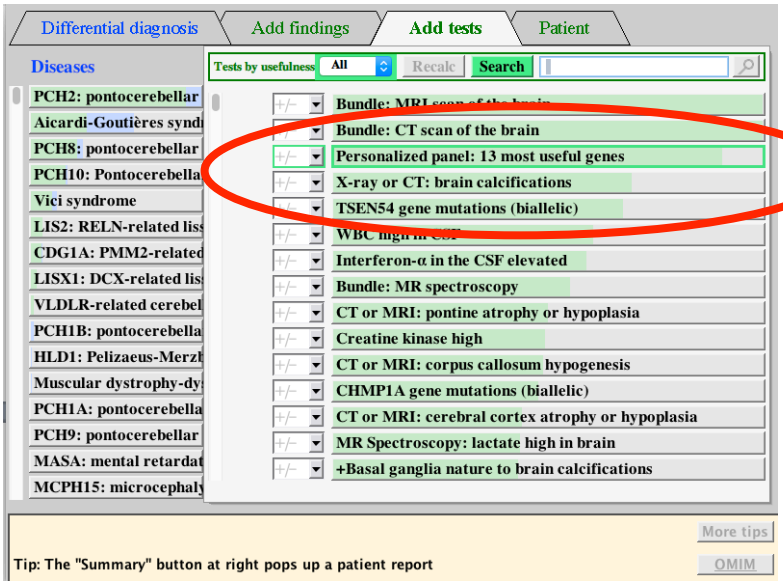
KEY	None or NA	Few is less than or equal to 30%	Some is more than 30%	Most is more than 85%

Generated on 25 May 2016 using software of 17 May 2016 and database of 17 May 2016.

PREMIUM UPGRADE OPTIONS: PERSONALIZED PANEL

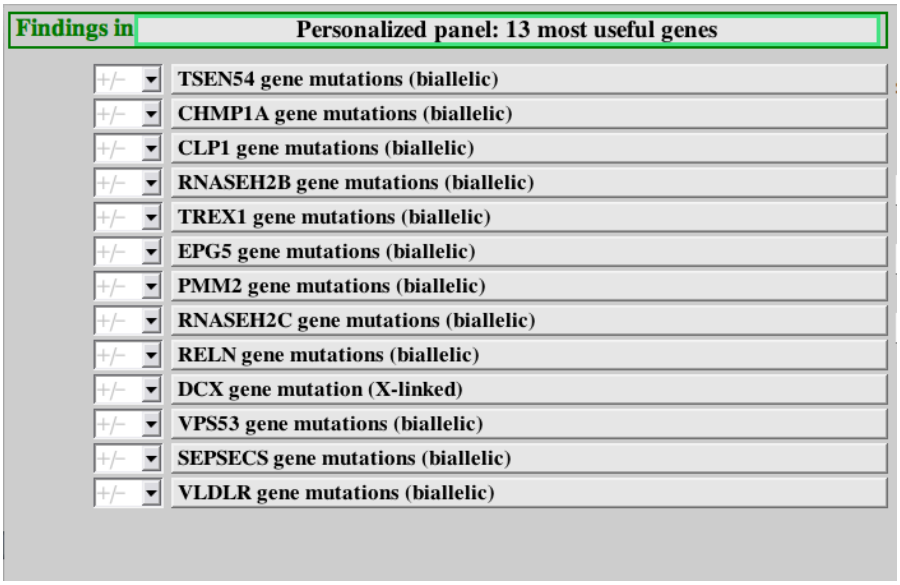
The Personalized Panel provides suggestions of the most important genes to order in the initial round of testing. If the list is long, it indicates consideration of large panels or an exome may be warranted. If short, Sanger-sequencing a few genes may an inexpensive route to an answer for this patient. The personalized panel also provides a list of the genes that must be well covered. For this reason, it can be helpful both to those ordering the tests and to the labs.

Figure 46: Personalized Panel in the Suggested Tests list



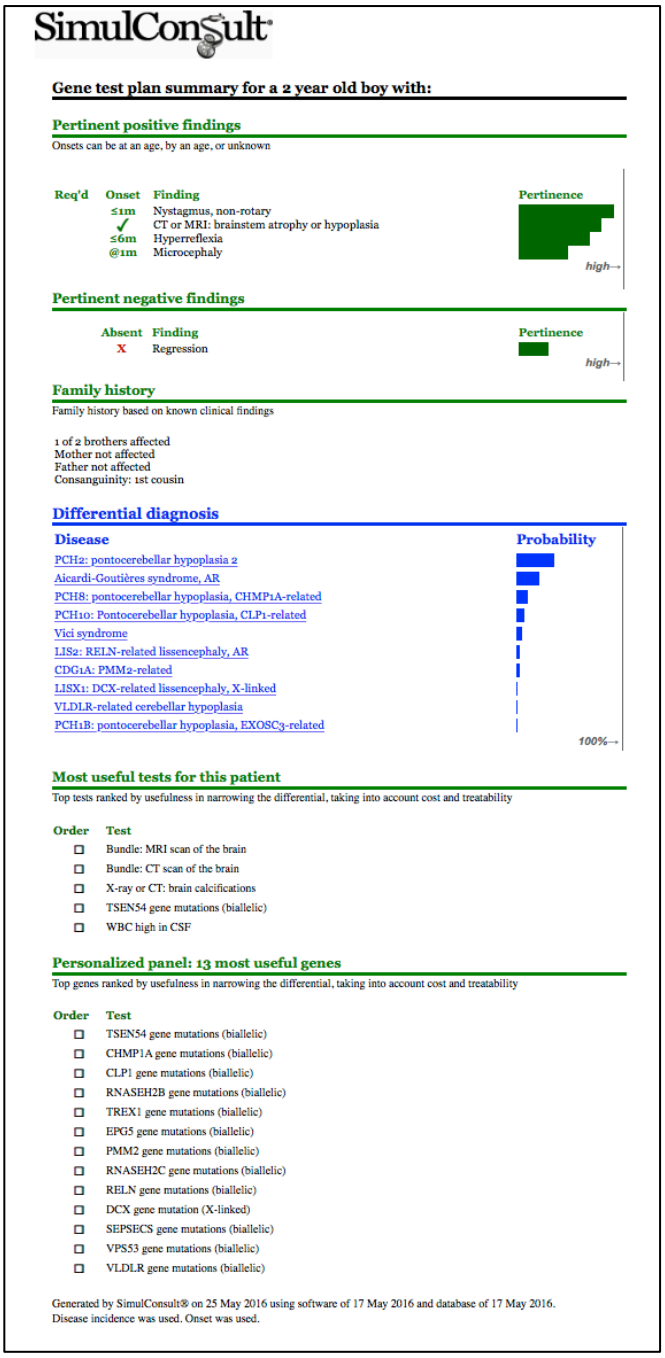
Clicking on the onset button shows the gene list.

Figure 47: Personalized Panel



The Personalized Panel is also added to the Patient Summary.

Figure 48: Patient Summary with Personalized Panel



SimulConsult

Gene test plan summary for a 2 year old boy with:

Pertinent positive findings

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

Req'd	Onset	Finding
	≤1m	Nystagmus, non-rotary
✓		CT or MRI: brainstem atrophy or hypoplasia
	≤6m	Hyperreflexia
	@1m	Microcephaly

Pertinence

high→

Pertinent negative findings

Absent	Finding
X	Regression

Pertinence

high→

Family history

Family history based on known clinical findings

1 of 2 brothers affected
Mother not affected
Father not affected
Consanguinity: 1st cousin

Differential diagnosis

Disease	Probability
PCH2: pontocerebellar hypoplasia 2	
Aicardi-Goutières syndrome, AR	
PCH8: pontocerebellar hypoplasia, CHMP1A-related	
PCH10: Pontocerebellar hypoplasia, CLP1-related	
Vici syndrome	
LIS2: RELN-related lissencephaly, AR	
CDG1A: PMM2-related	
LISX1: DCX-related lissencephaly, X-linked	
VLDLR-related cerebellar hypoplasia	
PCH1B: pontocerebellar hypoplasia, EXOSC3-related	

100%→

Most useful tests for this patient

Top tests ranked by usefulness in narrowing the differential, taking into account cost and treatability

Order	Test
☐	Bundle: MRI scan of the brain
☐	Bundle: CT scan of the brain
☐	X-ray or CT: brain calcifications
☐	TSEN54 gene mutations (biallelic)
☐	WBC high in CSF

Personalized panel: 13 most useful genes

Top genes ranked by usefulness in narrowing the differential, taking into account cost and treatability

Order	Test
☐	TSEN54 gene mutations (biallelic)
☐	CHMP1A gene mutations (biallelic)
☐	CLP1 gene mutations (biallelic)
☐	RNASEH2B gene mutations (biallelic)
☐	TREX1 gene mutations (biallelic)
☐	EPG5 gene mutations (biallelic)
☐	PMM2 gene mutations (biallelic)
☐	RNASEH2C gene mutations (biallelic)
☐	RELN gene mutations (biallelic)
☐	DCX gene mutation (X-linked)
☐	SEPSECS gene mutations (biallelic)
☐	VPS53 gene mutations (biallelic)
☐	VLDLR gene mutations (biallelic)

Generated by SimulConsult® on 25 May 2016 using software of 17 May 2016 and database of 17 May 2016.
Disease incidence was used. Onset was used.

INDEX OF FIGURES