

Basic features of SimulConsult

Diagnosis is one of the most complex intellectual tasks in medicine. Diagnosis requires taking knowledge about findings (symptoms, signs and test results) learned as “disease X has these findings” and inverting it to instead ask “with this group of findings, what diseases are likely”. The process of diagnosis is iterative – the diseases under consideration determine the most useful questions to ask next, the answers to which in turn affects the probability of the diseases under consideration in the differential diagnosis.

The SimulConsult Diagnostic Decision Support System (**DDSS**) aims to make each clinician **their best diagnostician**, while saving clinician time, (including accounting for the time to use the tool).

To do this, SimulConsult has curated medicine into a computational database. The database currently covers ~7,500 diseases, including genetic diseases with germline changes convincingly associated with human disease and all convincing chromosomal disorders. It also includes many nongenetic diseases, with particular strength in neurology and rheumatology.

The fundamental tasks performed by the DDSS are as follows:

- **Helps you collect findings.** Enables quick entry of patient findings – both pertinent positives and negatives (Figures 1 & 2).
- **Computes differential diagnosis.** Compares the findings you enter about your patient with every disease in the database and computes a measure of fit resulting in a probability-weighted list of possible diagnoses called a differential diagnosis.
- **Suggests useful findings.** Computes which among its ~10,000 findings would most change the differential diagnosis and displays these findings in rank order of Usefulness. When you specify the presence or absence of a finding, the software recalculates the differential diagnosis and useful findings iteratively each time a finding is entered.

Note: The DDSS **does not** use machine learning, but rather manual curation by expert clinicians. Machine learning is well-known to be bad at **unlearning**, which is a problem because our understanding of medicine continues to change. In addition, many subtle facts about rare diseases have never been written down and are only known to specialists.


Time course of findings. Critical to the performance of the DDSS is the fact that the database has the time course of each finding in each disease, and you specify the time course in your patient when you enter findings, when known. The DDSS then uses time-based Bayesian logic to do a pattern match.

Pertinent negatives. Diagnoses of exclusion and pertinent negatives are a critical part of genetic diagnosis; the DDSS allows you to specify that a finding is absent.

The main “Dx” screen. After you enter the patient age and sex, and an initial finding or findings from search or core lists, you will go to the main screen, “Dx” for diagnose. It has four tabs:

- **Differential.** This shows the evolving differential diagnosis (Figure 3) with the blue bars indicating probability
- **Add findings.** This displays clinical findings not yet commented on, in order of usefulness (Figures 4). The green shading indicates the finding's relative usefulness.
- **Add tests.** This displays test results not yet commented on, in order of usefulness. Instead of “All tests” (Figure 5) you can select to see only one kind of test. Some test “bundles” are shown (e.g., bone imaging in Figure 5) to combine the usefulness of all the results in the test.
- **Rule in or out.** By clicking “Rule in or out selected disease” in the Add findings or Add tests the usefulness assessment can focus on a particular disease (Figure 6).
- **Phenotype.** These are the findings you have entered about the patient, both pertinent positives and negatives.

Getting started using the software

Task	Description
Share button	The rightmost button on the top black navigation bar allows you to load or save a patient using either a PDF file that is both human and machine readable, or a Text string (Figure 7).
 Info buttons	These explain features and conventions in the software.
Hover over a disease or finding	If you hover over a disease or finding it will display the synonyms and explanatory terms.
Links	With a disease or a finding highlighted, click Links on the black top navigation bar to get links to relevant resources.
Two key colors	Green is associated with findings and blue with diseases

Entering information about the patient

Task	Description
Basic demographics	On the initial screen, you must enter the age and chromosomal sex of the patient to get started.
Family history	On the Initial screen, this feature allows you to specify if others in the family are affected, if known (Figure 8).
Primary, specialist or tertiary	On the initial screen, this feature allows you to ignore the incidence of the disease and is useful for when a patient has already had many commonly diagnosed conditions ruled out.
“O” Search	Click “O” on the top black navigation bar and then the Finding search tab. Then begin typing the name of a finding. A list of findings matching that term will appear. (Figure 2)
Core Lists	Click Core on the top black navigation bar. The lists of 48 core findings are available for several specialties, but most helpful in specialties for which patients are well described by 48 core findings, such as neurology or rheumatology. (Figure 1)
Presence / Absence	To the left of each finding is a pull-down menu with a “?” (once you’ve entered an age and sex for the patient). This is where you specify presence or absence. Include onset at an age or onset by an age to get maximum use of available data.
Required finding	Occasionally, a finding that is relatively common is so abnormal you want to be sure every disease you consider has that finding. The asterisk to the left of the presence display (when on the Search results and the Phenotype tab of the Dx screen) allows you to specify that a finding is required. Leaving a finding not required means the DDSS will consider the possibility of that finding being incidental to the diagnosis.

Assessing possible diseases

Task	Description
Differential diagnosis	All the tabs on the Dx screen show the differential diagnosis. The Phenotype tab on Dx shows the patient findings entered.
Profile	Click the button of the name of the disease and then click “Profile” up on the black bar to see all the findings in this disease, and click younger or older to see how they emerge over time
Assess	<p>With a disease selected, click “Assess” up on the black bar to see the fit between the patient and the information in the database about the disease – this is the reveal of the logic of the ranking in the differential diagnosis. Research has shown that DDSSs are only adopted if the physician can assess the logic, because no clinician wants to be in the position of answering the question “why did you diagnose x” with “the computer said so”.</p> <p>With a finding selected, click “Assess” up on the black bar to see the frequency of the finding in the diseases in the differential diagnosis.</p>

Saving and Reports

Task	Description
Text string	Automatically generate a text string that includes all the patient data (Figure 7). Pasting the text string into the Load field allows reopening the patient where you left off.
Summary report (findings only)	Assembles the pertinent positives and negatives and displays the HPO codes. The PDF is also machine readable, so you can pick up where you left off. The file can be generated from the Report menu (Figure 9) or the Share screen. It can be uploaded from the Share screen only (Figure 10).
Summary report (full)	Assembles the pertinent positives and negatives, differential diagnosis, and most useful tests into a graphical display. Document is also machine readable, so you can pick up where you left off. The file can be generated from the Report menu (Figure 11) or the Share screen. It can be uploaded from the Share screen only (Figure 12).
Prognosis table	Useful for Patient Education and communication between specialists and primary care. Characterizes the natural progression of the selected disease (without treatment).
SOAP note <i>(Subjective, Objective, Assessment and Plan)</i>	Automatically outputs a SOAP note format with the data you entered as plain text that can be copied and pasted to the electronic health record

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Figure 1: Genetics Core List

Notice that after commenting on the findings the green shading indicating usefulness will recalculate and lead you to the iteratively next most useful findings based on the differential.

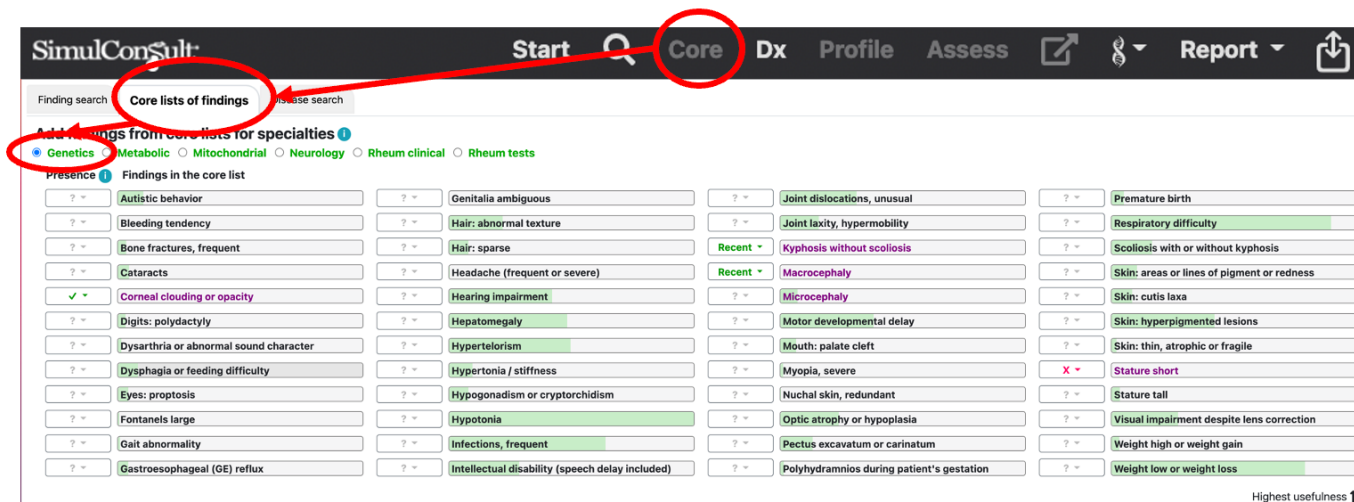
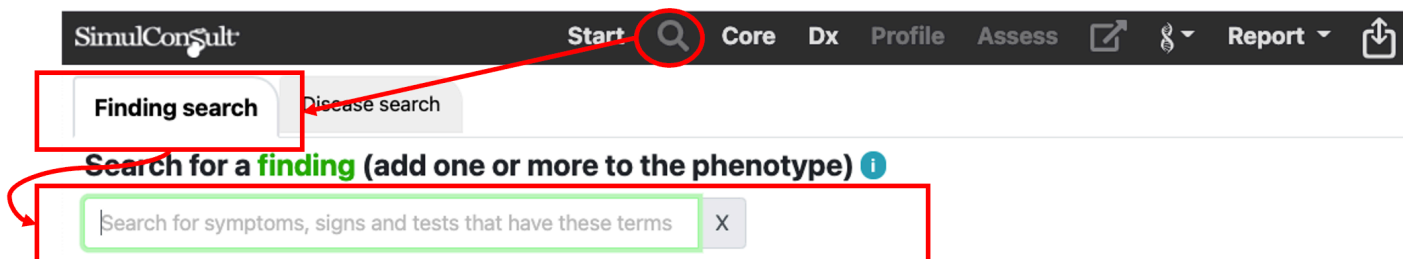


Figure 2: Search for finding



Next: Click Dx (Diagnose) on the top black navigation bar for differential diagnosis

The Dx screen is the core of the software. Use its capabilities, **Q** or **Core** to keep adding findings until you are satisfied with the diagnosis or workup.

The top black navigation bar provides access to other screens, including **U** for loading a previous patient or saving the current patient.

Figure 3: Dx/Differential

SimulConsult Start Core Dx Profile Assess Report

Differential Add findings Add tests Phenotype 3 1

Diseases ranked by probability

- MPS I, severe: Hurler syndrome classic
- Acromesomelic dysplasia, Maroteaux type
- NF1: Neurofibromatosis 1
- MPS VII: Sly syndrome, infantile
- GM1 gangliosidosis, type I (infantile)
- Sialidosis II, infantile
- Schimmelpenning-Feuerstein-Mims syndrome
- MPS VI A (classic, severe): Maroteaux-Lamy syndrome
- MPS IV A (Morquio, GALNS-related)
- Sjögren-Larsson syndrome
- Kabuki syndrome 1
- Mucopolipidosis III α/β
- MPS II A (severe): Hunter syndrome
- Hypomelanosis of Ito
- MPS VI B (intermediate): Maroteaux-Lamy syndrome
- MPS VI C (mild): Maroteaux-Lamy syndrome
- Ichthyosis X-linked
- Cockayne syndrome I, moderate or classic
- Multicentric osteolysis nodulosis and arthropathy
- GLC3A: CYP1B1-related primary congenital glaucoma

Top < 1 of all diseases > 100% probability ↑

Figure 4: Add findings by usefulness

SimulConsult Start Core Dx Profile Assess Report

Differential **Add findings** Add tests Phenotype 3 1

MPS I, severe: Hurler syndro...

Acromesomelic dysplasia, Ma...

NF1: Neurofibromatosis 1

MPS VII: Sly syndrome, infant...

GM1 gangliosidosis, type I (in...

Sialidosis II, infantile

Schimmelpenning-Feuerstein...

MPS VI A (classic, severe): M...

MPS IV A (Morquio, GALNS-re...

Sjögren-Larsson syndrome

Kabuki syndrome 1

Mucopolipidosis III α/β

MPS II A (severe): Hunter syn...

Hypomelanosis of Ito

MPS VI B (intermediate): Mar...

MPS VI C (mild): Maroteaux-L...

Ichthyosis X-linked

Cockayne syndrome I, moder...

Multicentric osteolysis nodul...

GLC3A: CYP1B1-related prim...

Top < 1 >

Presence i **Findings ranked by usefulness** i

? ▾	Hypotonia
? ▾	Mouth: tonsils large
? ▾	Respiratory difficulty
? ▾	Eyebrows thick
? ▾	Epicanthus
? ▾	Face, coarse features
? ▾	Mouth: alveolar ridge overgrowth
? ▾	Weight low or weight loss
? ▾	Peripheral nerve entrapment or compression
? ▾	Lip: vermilion, upper lip, thick
? ▾	Frontal bossing
? ▾	Lip: vermilion, lower lip, thick
? ▾	Mouth: tongue large
? ▾	Atlantoaxial instability or dislocation
? ▾	Sleep apnea
? ▾	Dolichocephaly
? ▾	Infections, frequent
? ▾	Hernia of the abdominal wall
? ▾	Skin: epidermal thickening

Top < 1 of all findings > Highest usefulness ↑

Figure 5: Add tests by usefulness

SimulConsult Start Core Dx Profile Assess Report

Differential Add findings **Add tests** Phenotype 3 1

All tests

Presence i **Tests ranked by usefulness** i

? ▾	α-L-iduronidase enzyme low or absent
? ▾	Heparan sulfate high in non-dilute urine
? ▾	Dermatan sulfate high in non-dilute urine
Bundle ▾	Bone imaging
Bundle ▾	Blood smear (peripheral)
? ▾	IDUA gene variants (biallelic)
? ▾	Blood cell metachromasia on toluidine blue staining
? ▾	X-ray: dysostotic thickening of long bones
? ▾	Lymphocytes: abnormal light microscopy on peripheral blood smear
Bundle ▾	CT scan of the head
? ▾	Neutrophils: granulocytes with inclusions or granules on peripheral blood smear
? ▾	Imaging: bone diaphysis abnormal
Bundle ▾	MRI scan of the brain
Bundle ▾	Conjunctival biopsy
? ▾	Conjunctival biopsy: abnormal EM morphology
? ▾	Pigmentary retinopathy
? ▾	X-ray: vertebrae abnormal
Bundle ▾	Echocardiogram

Top < 1 > Highest usefulness ↑

Figure 6: Rule in or Rule out a disease

SimulConsult Start Core Dx Profile Assess Report

Differential **Add findings** Add tests Phenotype 3 1

Usefulness in all diseases Rule in or out selected disease

Presence i Findings ranked by usefulness i

? ▾	Limbs very short or absent
? ▾	Digits: toes short
? ▾	Foot, short
? ▾	Digits: fingers short or stubby
? ▾	Palm, short
? ▾	Nails, short
? ▾	Ulna short, hypoplastic, deformed or absent
? ▾	Radius short, hypoplastic, deformed or absent
? ▾	Metacarpal bone short, hypoplastic or absent
? ▾	Digits: finger, proximal phalanx short or absent
? ▾	Digits: finger, middle phalanx short or absent
? ▾	Humerus short, hypoplastic, deformed or absent
? ▾	Bowing of long bones
? ▾	Joint laxity, hypermobility
? ▾	Digits: finger, distal phalanx short or absent
? ▾	Lumbar hyperlordosis
? ▾	Skin: cutis laxa
? ▾	Contractures or limited range of motion
? ▾	Nose: short

Top < 1 > Highest usefulness ↑

Figure 7: Patient Summary Text String

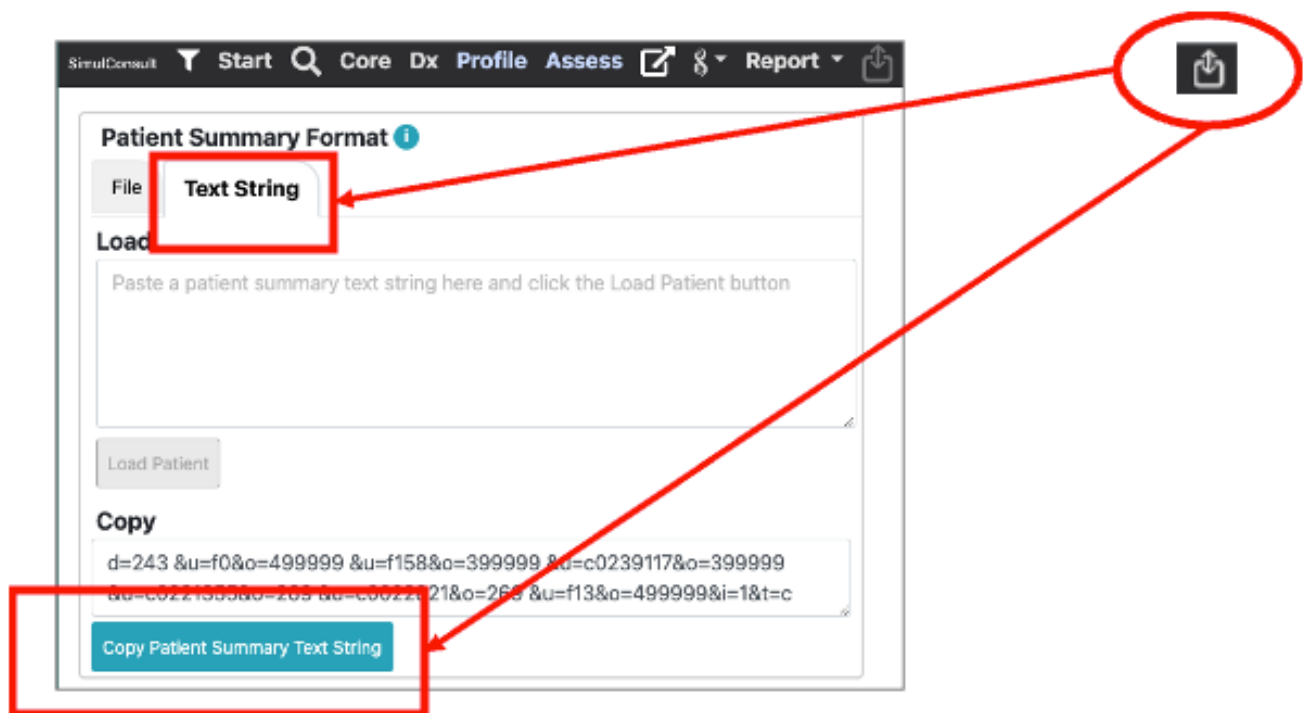


Figure 8: Add family history

The screenshot displays the SimulConsult web interface. At the top, a navigation bar includes the 'Start' button, which is highlighted with a red box. Below the navigation bar, the 'Required information about this patient' section contains fields for Age (8), Sex (Male), and a 'Next' instruction. The 'Optional information about this patient' section is expanded, showing a list of checkboxes: 'Emerged over...', 'Family history', 'Exposure history', and 'Died'. The 'Family history' checkbox is selected and highlighted with a red box. A red arrow points from the 'Start' button to this checkbox. A blue checkmark icon is located to the left of the 'Family history' checkbox. The expanded 'Family history' section includes a yellow background area with the following options: 'Mother affected' (Unknown, No, Yes), 'Father affected' (Unknown, No, Yes), 'Sisters affected' (0 of 0 by similar age), 'Brothers affected' (0 of 0 by similar age), 'Maternal uncles affected' (0 of 0 total), and 'Parental consanguinity' (none noted). Below this, there are checkboxes for 'Exposure history' and 'Died'. The 'Settings for this patient' section shows 'Care level' (Primary, Specialist, Tertiary) and 'Onset considered' (checked). The 'About the software' section provides details on the software's capabilities and licensing.

Figure 9: Patient Summary (Findings only) to generate PDF and save

The screenshot displays the SimulConsult interface for a patient named Lynn Feldman. The top navigation bar includes 'Initial', 'Dx', 'Profile', 'Assess', 'Links', and 'Report'. The 'Report' dropdown menu is open, showing options: 'Chart note (findings only)', 'Chart note (SOAP format)', 'Summary report (findings only)', 'Summary report (full)', 'Genome report', and 'Prognosis table for active disease'. The 'Summary report (findings only)' option is selected. Below the navigation, there are tabs for 'Finding search', 'Core lists of findings', and 'Disease search'. The main area is titled 'Add findings from core lists for specialties' with radio buttons for 'Genetics', 'Metabolic', 'Mitochondrial', 'Neurology', 'Rheum clinical', and 'Rheum tests'. A grid of findings is shown, with 'Stature short' highlighted in green and marked with an 'X'. A 'Summary by Lynn Feldman for the 8 month old boy with findings:' section is visible, containing a PDF icon. Two inset boxes show the generated PDF content, which includes 'Pertinent positive findings' and 'Pertinent negative findings' with associated bar charts and text.

Summary by Lynn Feldman for the 8 month old boy with findings:

Pertinent positive findings
Onsets can be at an age, by an age, or unknown

Req'd	Onset	Finding	Pertinence
Recent		Kyphosis without scoliosis HP:000808	High
	✓	Corneal clouding or opacity HP:000759	High
Recent		Macrocephaly HP:000026	High

Pertinent negative findings

Absent	Finding	Pertinence
X	Stature short HP:000432	High

Generated by SimulConsult® on 29 April 2021 17:36 using interface of 2021 April 29 14:50, algorithms of 2021 April 29 14:40 and database of 27 April 2021 19:07. All times are UTC. Care setting was primary. Onset was used.

SimulConsult Summary by Lynn Feldman for the 8 month old boy with findings:

Pertinent positive findings
Onsets can be at an age, by an age, or unknown

Req'd	Onset	Finding	Pertinence
Recent		Kyphosis without scoliosis HP:000808	High
	✓	Corneal clouding or opacity HP:000759	High
Recent		Macrocephaly HP:000026	High

Pertinent negative findings

Absent	Finding	Pertinence
X	Stature short HP:000432	High

This information about the patient can be re-loaded into the SimulConsult software using the PDF file. To do so, open the software and use the rightmost option on the black top navigator bar to load this file. The disease probabilities and the finding pertinence may change due to changes in knowledge in the SimulConsult database. This file was generated by SimulConsult® on 29 April 2021 17:40 using interface of 2021 April 29 14:50, algorithms of 2021 April 29 14:40 and database of 27 April 2021 19:07. All times are UTC. Care setting was primary. Onset was used.

Figure 10: Patient Summary (Findings only) upload

SimulConsult Initial Dx Profile Assess Links Report

Patient Summary Format ?

File | Text String

Load

(load a Summary Report in PDF or HTML format)

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

Select the file to upload

Choose Files to Upload			
Other			
	Size	Kind	Date Added
summary-findings-Patient 123456.pdf	48 KB	PDF Document	Today at 11:38 AM
summary-findings-Patient 654321.pdf	48 KB	PDF Document	Today at 11:38 AM

Cancel Upload

PDF file

SimulConsult
Resumed by Last Findings for the 8 month old boy with findings

Perform positive findings
Create one for each sign, symptom, or observation

Findings	Present	Performance
Respiratory distress	<input type="checkbox"/>	<input type="checkbox"/>
Central cyanosis or sperry	<input type="checkbox"/>	<input type="checkbox"/>
Stridor	<input type="checkbox"/>	<input type="checkbox"/>
Wheezing	<input type="checkbox"/>	<input type="checkbox"/>

Perform negative findings

Findings	Present	Performance
Stridor	<input type="checkbox"/>	<input type="checkbox"/>

This information about the patient can be re-loaded into the SimulConsult software using the PDF file. To do so, open the software and use the rightmost option on the back navigation bar to load this file. The success or otherwise and the timing performance may change as an integral knowledge in the SimulConsult database. This file was generated by SimulConsult on 28 April 2021 17:46 using version of 2021 April 28 14:10; updates of 2021 April 28 14:40 and releases of 27 April 2021 16:07. All times are UTC. Core settings were primary. Check user mail.

Figure 11: Patient Summary (Full) generate and save

Summary by Lynn Feldman for the 8 month old boy with findings:

Pertinent positive findings
 Onsets can be at an age, by an age, or unknown
 Recent Kyphosis without scoliosis
 ✓ Corneal clouding or opacity
 Recent Macrocephaly

Pertinent negative findings
 Absent Finding Persistence
 X Stature short

Differential diagnosis
 Disease Probability
 MPS I, severe; Hunter syndrome (class)
 Anomalous; Ehlers-Danlos, Marfan type
 MPS VI; Neurofibromatosis 1
 MPS VII; Sly syndrome, infantile
 GM1 gangliosidosis, type I (infantile)
 Shukhov II, infantile
 Schimмельpenning-Ferretius-Mina syndrome
 MPS VI A (classic, severe); Marfan-Lamy syndrome
 MPS IV A (Shugarin, GALNS-related)
 Sjögren-Larsson syndrome

Most useful tests for this patient
 Top tests ranked by usefulness in narrowing the differential, taking into account cost and feasibility

Order Test
 α-L-iduronidase enzyme low or absent
 Heparan sulfate high in non-dilute urine
 Dermatan sulfate high in non-dilute urine
 Bundle: Bone imaging
 Bundle: Blood smear (peripheral)

Generated by SimuConsult® on 29 April 2021 17:59 using interface of 2021 April 29 14:50, algorithms of 2021 April 29 14:40 and database of 27 April 2021 19:07. All times are UTC. Care setting was primary. Onset was used.

PDF File

SimuConsult
 Summary by Lynn Feldman for the 8 month old boy with findings:

Pertinent positive findings
 Onsets can be at an age, by an age, or unknown
 Recent Kyphosis without scoliosis
 ✓ Corneal clouding or opacity
 Recent Macrocephaly

Pertinent negative findings
 Absent Finding Persistence
 X Stature short

Differential diagnosis
 Disease Probability
 MPS I, severe; Hunter syndrome (class)
 Anomalous; Ehlers-Danlos, Marfan type
 MPS VI; Neurofibromatosis 1
 MPS VII; Sly syndrome, infantile
 GM1 gangliosidosis, type I (infantile)
 Shukhov II, infantile
 Schimмельpenning-Ferretius-Mina syndrome
 MPS VI A (classic, severe); Marfan-Lamy syndrome
 MPS IV A (Shugarin, GALNS-related)
 Sjögren-Larsson syndrome

Most useful tests for this patient
 Top tests ranked by usefulness in narrowing the differential diagnosis, taking into account cost and feasibility

Order Test
 α-L-iduronidase enzyme low or absent
 Heparan sulfate high in non-dilute urine
 Dermatan sulfate high in non-dilute urine
 Bundle: Bone imaging
 Bundle: Blood smear (peripheral)

This information about the patient can be tracked into the SimuConsult software using this PDF file. To do so, open the software and use the rightmost button on the back log navigation bar to save this file. The disease probabilities and the finding persistence may change due to changes in knowledge in the SimuConsult database. This file was generated by SimuConsult® on 29 April 2021 18:01 using interface of 2021 April 29 14:50, algorithms of 2021 April 29 14:40 and database of 27 April 2021 19:07. All times are UTC. Care setting was primary. Onset was used.

Figure 12: Patient Summary (Full) upload

The screenshot shows the SimulConsult interface for uploading a Patient Summary. The top navigation bar includes 'Initial', 'Dx', 'Profile', 'Assess', 'Links', and 'Report'. A red circle highlights an upload icon in the top right. Below, the 'Patient Summary Format' section has a 'File' button circled in red. A red arrow points from this button to a 'Browse' button in the 'Load' section, which is also circled in red. The 'Load' section contains a text input field with the placeholder '(load a Summary Report in PDF or HTML format)' and a 'Browse' button. Below this, text explains that PDF files are used to resume patients and that HTML versions from older software are also acceptable. A red arrow points from the 'Browse' button to a file selection dialog titled 'Choose Files to Upload'. This dialog shows a table of files:

	Size	Kind	Date Added
summary-findings-Patient 123456.pdf	48 KB	PDF Document	Today at 11:38 AM
summary-findings-Patient 654321.pdf	48 KB	PDF Document	Today at 11:38 AM

Below the table are 'Cancel' and 'Upload' buttons. A red arrow points from the 'Upload' button to a preview of a PDF file, labeled 'PDF file'.