

What you need to know even if you hate reading manuals!

(by Rolf H. Sijmons, MD, PhD, August 20th 2008)

I. The Basics (skip this if you are an expert on familial cancer).

This database assumes that you have at least some basic knowledge of the clinical aspects of inherited cancer predisposition that will help you in selecting from your patient's and/or family's history those tumors and non-tumor features that are the best search handles. Especially for the non-clinicians, who may want to take a look at the database for scientific purposes, we briefly introduce the basics of that process here:

First, try to select only those tumor features observed in a patient/family which are suggestive of an inherited predisposition. This is important because cancer is of course a very common disease and therefore pedigrees of families with hereditary cancer may also show relatives with non-hereditary cancer which may cloud the typical pattern of the hereditary cancer syndromes in those pedigrees.

The following features are suggestive of an inherited cancer predisposition, especially if they are found in combination:

- cancer with a early age of onset for that type of cancer
- multiple primary tumors (in the same or in different organs)
- cancer occurring in successive generations
 - o Most cancer syndromes are autosomal dominant, however, some are autosomal recessive and X-linked. In addition, less than 100% penetrance, *de novo* mutations and non-paternity may cause atypical patterns in families for autosomal dominant disorders. For all these reasons, a negative family history of cancer does not exclude the diagnosis hereditary cancer in a patient.
- cancer occurring in the not-typical gender for that tumor
 - o e.g. breast cancer in males
- certain rare types of cancer
 - o e.g. retinoblastoma, medullary thyroid cancer).
 - o the reverse is not true: the most frequent hereditary tumors are of a common type, like colorectal, breast, ovarian, prostate and endometrial cancer)
- cancer in the presence of many precursor lesions
 - o e.g. adenomatous colorectal polyps
- cancer occurring in the absence of well-known risk factors
 - o e.g. lung cancer in a non-smoker
- cancer occurring in the presence of dysmorphic features/congenital anomalies
- cancer in a patient/family with a diagnosed hereditary disorder
 - o consider a possible link between the two.

Next, in addition to patterns of cancer in the family, the *absence* of reported cancer in relatives is taken into account as well. This is something an expert usually does by looking at the pedigree, taking into account the size of the family in the different generations, the gender of the relatives, the ages they reached and the possible

modes of inheritance. The clinician's own experience/knowledge or other resources like for example FaCD searches might lead to expanding the questions asked to patients and their families, e.g. for the occurrence of pneumothorax or myomas in families with early onset renal cancer (check FaCD if these questions do not ring any clinical bells). Other possible steps in the diagnostic process include examining the medical details/confirmation of the reported cancers and other disorders of interest, results from physical examination (e.g. looking for cutaneous signs of particular tumor syndromes) and results from lab tests (e.g. DNA), radiological and sometimes genealogical studies. Usually, in the end, a diagnosis will be made or at least the differential diagnosis will be narrowed down.

II. Working with the database

(1) Adding symptoms to the Selected symptoms list

Click on the Find Syndromes item in the main menu. You can now select symptoms from the dropdown list in the *Symptoms by system* menu. Clicking on Add will add the selected symptom to the *Selected symptoms* box on the right.

Find syndromes		How to search for syndromes	
Symptoms by System		<input type="button" value="Find symptoms"/>	Selected symptoms
Cardiovascular System	Heart	[No symptoms selected yet]	
Tumor symptoms cardiac fibroma Add cardiac myxoma Add cardiac rhabdomyoma Add cardiac tumor Add	Non-tumor symptoms heart, congenital defect Add myocardial disease Add pericardial constriction Add	<input type="button" value="Find narrow"/>	<input type="button" value="Find wide"/>

Alternatively, you can press the *Find symptoms* button and type the name of symptom you are looking for, or just a part of that name, in the search box, as shown below for 'colo'. Next, press the *Find Symptom* button or simply press <enter> on your keyboard and select the symptom of your choice by clicking on *Add*.

Find syndromes		How to search for syndromes	
All symptoms		<input type="button" value="Show symptoms by system"/>	Selected symptoms
colo	<input type="button" value="Find Symptom"/>	[No symptoms selected yet]	
SymptomName colon cancer Add colonic lipoma Add colorectal adenomas Add colorectal adenomatous polyps Add colorectal cancer Add colorectal carcinoid Add colorectal hamartomas Add colorectal hyperplastic polyps Add colorectal neuromas Add colorectal polyps Add colorectal stromal tumor Add colorectal tumor Add eye, coloboma of the Add hamartomatous polyps in colon/rectum Add serrated adenomas, colorectal Add		<input type="button" value="Find narrow"/>	<input type="button" value="Find wide"/>

If you are unhappy with your selection, then click on the *trash can* next to the symptoms that you want to delete from your list, or press the *Reset list* button to delete them all at once.

Selected symptoms

Selected symptom	Ignore
breast cancer	<input type="checkbox"/> 
colon cancer	<input type="checkbox"/> 
lung/bronchial cancer	<input type="checkbox"/> 

Find syndromes with

(2) The way FaCD handles multiple search terms.

If you enter more than one item in the *Selected symptoms* list, e.g. breast cancer, colorectal cancer and lung cancer, then FaCD will by default **only** select those disorders which match **all** of the search terms (*i.e.* immunodeficiency as well as hepatic tumors). You can 'play' with your search profile by checking the *Ignore* option for different search terms and then run the search again.

Find syndromes
How to search for syndromes

Symptoms by System	Find symptoms	Selected symptoms																												
Respiratory System ▼ Lower respiratory tract ▼		<table border="1"> <thead> <tr> <th>Selected symptom</th> <th>Ignore</th> </tr> </thead> <tbody> <tr> <td>breast cancer</td> <td><input type="checkbox"/> </td> </tr> <tr> <td>colorectal cancer</td> <td><input type="checkbox"/> </td> </tr> <tr> <td>lung/bronchial cancer</td> <td><input type="checkbox"/> </td> </tr> </tbody> </table> <p><input type="button" value="Reset list"/></p> <p>Find syndromes with</p> <p>all ▼ non-ignored symptoms</p> <p><input type="button" value="Find narrow"/> <input type="button" value="Find wide"/></p>	Selected symptom	Ignore	breast cancer	<input type="checkbox"/> 	colorectal cancer	<input type="checkbox"/> 	lung/bronchial cancer	<input type="checkbox"/> 																				
Selected symptom	Ignore																													
breast cancer	<input type="checkbox"/> 																													
colorectal cancer	<input type="checkbox"/> 																													
lung/bronchial cancer	<input type="checkbox"/> 																													
<table border="0"> <thead> <tr> <th style="text-align: left;">Tumor symptoms</th> <th style="text-align: left;">Non-tumor symptoms</th> </tr> </thead> <tbody> <tr> <td>bronchioli, leiomyoma of the Add</td> <td>abnormal lung lobulation Add</td> </tr> <tr> <td>carcinoid of bronchus Add</td> <td>asthma Add</td> </tr> <tr> <td>carcinoid of the lung Add</td> <td>COPD Add</td> </tr> <tr> <td>lung cystadenoma Add</td> <td>lung cysts Add</td> </tr> <tr> <td>lung hemangioma Add</td> <td>lung emphysema Add</td> </tr> <tr> <td>lung, alveolar cell cancer Add</td> <td>lung fibrosis Add</td> </tr> <tr> <td>lung/bronchial cancer Add</td> <td>lung hypoplasia Add</td> </tr> <tr> <td>lung/bronchial tumor Add</td> <td>lung, honeycomb fibrosis of the Add</td> </tr> <tr> <td>malignant fibrous histiocytoma of the lung Add</td> <td></td> </tr> <tr> <td>pleuropulmonary blastoma Add</td> <td></td> </tr> <tr> <td>pulmonary chondroma Add</td> <td></td> </tr> <tr> <td>pulmonary hamartoma Add</td> <td></td> </tr> <tr> <td>pulmonary lymphangioleiomyomatosis Add</td> <td></td> </tr> </tbody> </table>	Tumor symptoms	Non-tumor symptoms	bronchioli, leiomyoma of the Add	abnormal lung lobulation Add	carcinoid of bronchus Add	asthma Add	carcinoid of the lung Add	COPD Add	lung cystadenoma Add	lung cysts Add	lung hemangioma Add	lung emphysema Add	lung, alveolar cell cancer Add	lung fibrosis Add	lung/bronchial cancer Add	lung hypoplasia Add	lung/bronchial tumor Add	lung, honeycomb fibrosis of the Add	malignant fibrous histiocytoma of the lung Add		pleuropulmonary blastoma Add		pulmonary chondroma Add		pulmonary hamartoma Add		pulmonary lymphangioleiomyomatosis Add			
Tumor symptoms	Non-tumor symptoms																													
bronchioli, leiomyoma of the Add	abnormal lung lobulation Add																													
carcinoid of bronchus Add	asthma Add																													
carcinoid of the lung Add	COPD Add																													
lung cystadenoma Add	lung cysts Add																													
lung hemangioma Add	lung emphysema Add																													
lung, alveolar cell cancer Add	lung fibrosis Add																													
lung/bronchial cancer Add	lung hypoplasia Add																													
lung/bronchial tumor Add	lung, honeycomb fibrosis of the Add																													
malignant fibrous histiocytoma of the lung Add																														
pleuropulmonary blastoma Add																														
pulmonary chondroma Add																														
pulmonary hamartoma Add																														
pulmonary lymphangioleiomyomatosis Add																														

Another approach is to have FaCD search the syndrome database for syndromes that do not necessarily feature all of the selected symptoms. For example, by looking for syndromes that have 2 or more of the symptoms from your *Selected symptoms* list. Simply select the option from the dropdown menu as shown below. The number of options depends on the number of symptoms in your list,

How to search for syndromes

toms

Selected symptoms

Selected symptom	Ignore
breast cancer	<input type="checkbox"/>
colorectal cancer	<input type="checkbox"/>
lung/bronchial cancer	<input type="checkbox"/>

Reset list

Find syndromes with

all non-ignored

all

2 or more

1 or more

Find wide

Use of the *Find narrow* and *Find wide* buttons is explained in the next section.

(3) Narrow and Wide searches. The way FaCD differentiates between certain and uncertain associations.

Especially in rare disorders it may be uncertain if certain findings are truly associated or merely coincidental. The database includes those uncertain features and has labeled them as 'possible features' thereby differentiating them from the features of which we are certain or at least fairly certain that they are a clinical manifestation of the disorders. You may choose to search FaCD for certain **as well as** possible associations (a '**wide**' search) or search **only** for certain associations (a '**narrow**' search). Press either the *Find narrow* or the *Find wide* button to start searching the database for matching syndromes.

(4) Broad search terms and broad diagnostic terms: they look similar but have different meaning.

I. Searching for syndromes

FaCD offers several **broad search terms** to deal with a family history before verification has been completed and all medical details are known. For example, it is not uncommon for a family to report 'gastrointestinal cancer' in one of their relatives, not knowing precisely which organ was affected. Searching for disorders with the term 'gastrointestinal cancer', will select all disorders with **one or more** types of gastrointestinal cancer. If you know the exact tumor type (e.g. gastric cancer) then using its name as a search term would of course give a more focused selection.

II. Reading syndrome details

If you look at the clinical description of the disorders in the database, then some of those disorders will list **broad diagnostic terms**, e.g. 'gastrointestinal cancer'. In those cases this means that **all** features covered by those broad terms are indeed part of the clinical manifestations of those disorders (we did this in order to shorten the lists in the clinical details screens). The exceptions to this rule are the disorders in which a category is reported in the literature without any further specification (e.g.the patient with disorder X suffered from 'acute leukemia'.....no subtype mentioned.....). These exceptions can be identified by reading the clinical synopsis ('Comment' in the 'Syndrome Details' screens).

III. Consulting other sources. Disclaimer.

The familial cancer database is an expert-support system. It is meant to support the making of a genetic differential diagnosis in cancer patients and families, as well as in making clinicians aware of the tumor types that have been reported as complications of particular genetic conditions (e.g. Noonan syndrome or Cystic Fibrosis). FaCD is not a substitute for consulting an expert on familial cancer.