

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		Selected symptoms	
<input type="text" value="Cardiovascular System"/> <input type="button" value="Find symptoms"/>		<input type="text" value="Heart"/> <input type="button" value="Find narrow"/> <input type="button" value="Find wide"/>	
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	[No symptoms selected yet]	

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		Selected symptoms	
<input type="text" value="colo"/> <input type="button" value="Find Symptom"/>		<input type="button" value="Show symptoms by system"/>	
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		[No symptoms selected yet]	
		<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

Respiratory System Lower respiratory tract

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		

Selected symptoms

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

Find syndromes with

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

<input type="text" value="toms"/> <input type="button" value="Add"/> <input type="button" value="Add"/> <input type="button" value="Add"/> <input type="button" value="Add"/> <input type="button" value="Add"/> <input type="button" value="Add"/> <input type="button" value="Add"/>	<p>Selected symptoms</p> <table border="1"> <thead> <tr> <th>Selected symptom</th> <th>Ignore</th> </tr> </thead> <tbody> <tr> <td>breast cancer</td> <td><input type="checkbox"/> <input type="button" value="🗑️"/></td> </tr> <tr> <td>colorectal cancer</td> <td><input type="checkbox"/> <input type="button" value="🗑️"/></td> </tr> <tr> <td>lung/bronchial cancer</td> <td><input type="checkbox"/> <input type="button" value="🗑️"/></td> </tr> </tbody> </table> <p style="text-align: center;"><input type="button" value="Reset list"/></p> <hr/> <p>Find syndromes with</p> <table border="1"> <tr> <td>all</td> <td>non-ignored</td> </tr> <tr> <td>all</td> <td></td> </tr> <tr> <td>2 or more</td> <td></td> </tr> <tr> <td>1 or more</td> <td></td> </tr> </table> <p style="text-align: right;"><input type="button" value="Find wide"/></p>	Selected symptom	Ignore	breast cancer	<input type="checkbox"/> <input type="button" value="🗑️"/>	colorectal cancer	<input type="checkbox"/> <input type="button" value="🗑️"/>	lung/bronchial cancer	<input type="checkbox"/> <input type="button" value="🗑️"/>	all	non-ignored	all		2 or more		1 or more	
Selected symptom	Ignore																
breast cancer	<input type="checkbox"/> <input type="button" value="🗑️"/>																
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all	non-ignored																
all																	
2 or more																	
1 or more																	

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.