ICABME 2019 Lebanese University
Order of Engineering
Tripoli - Lebanon
October 17,19 2019
5th International Conference
on Advances in Biomedical Engineering

Hierarchical visual case-based reasoning for supporting breast cancer therapy

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This work was funded by the European Union's Horizon 2020 research and innovation program under grant agreement No 690238.

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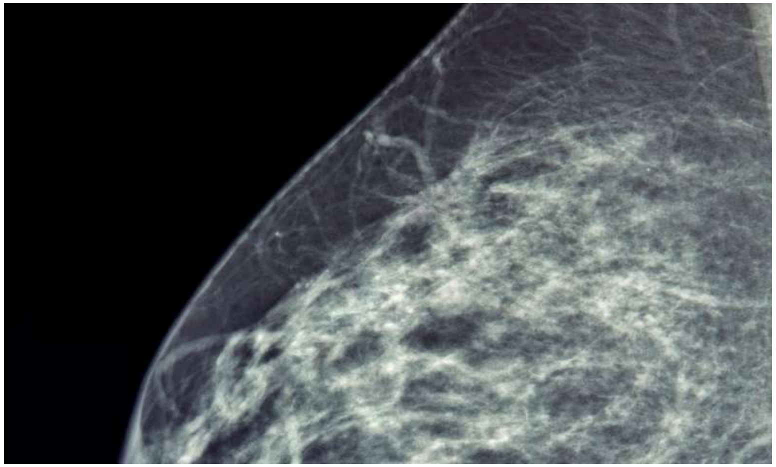
Introduction

- **Breast cancer**
  - One of the most common types of cancer that affects women in Europe
  - High survival rate at 10 years

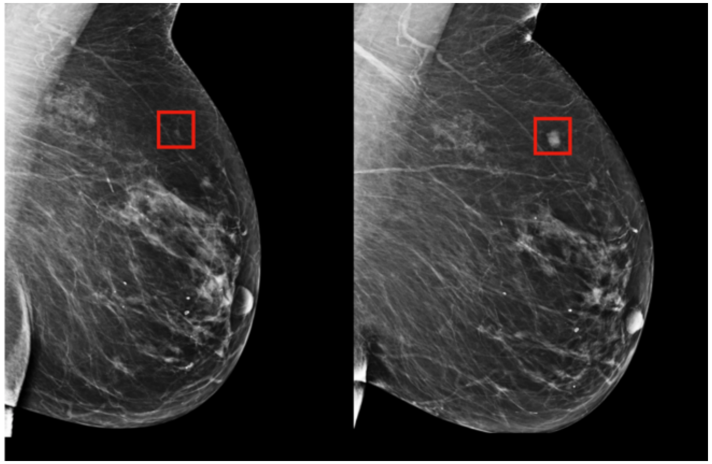


Source: MedicalXPress

- **Artificial Intelligence supports the diagnostic of breast cancer**
  - Deep learning
  - SVM
  - Image analysis
- **But supporting the therapy is more complex !!!**
  - Many treatments exist, with 4 main categories:
    - surgery, chemotherapy, endocrine therapy and radiotherapy
  - Many clinical data need to be considered
    - Clinical data are often not structured, contrary to medical images
  - Difficult to produce a learning base
    - For a patient, the best treatment is never known

Introduction

- **The problem of explanations**
  - Physicians need to understand the rationale of a recommendation in order to follow it
  - For diagnosis systems, an annotated image can make a decent explanation



Source: MIT

  - But for therapy, explanations are much more difficult to produce
    - And time is limited (3 minutes per patient in breast cancer unit)

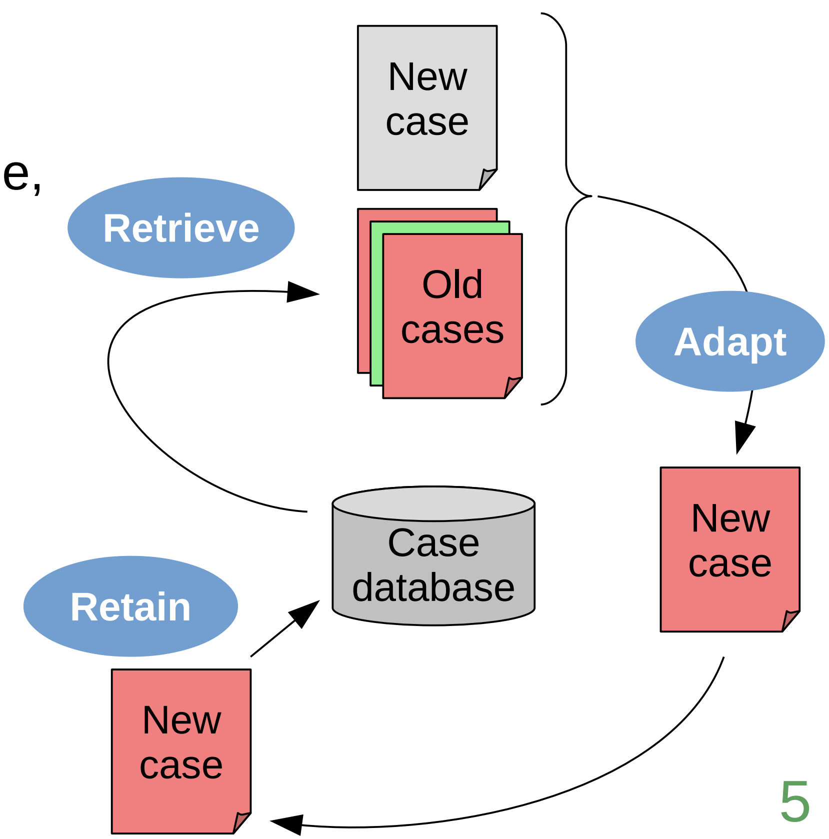
- **=> Explainable Artificial Intelligence (XAI)**

Introduction

- **The DESIREE European H2020 project**
  - **Decision Support and Information Management System for Breast Cancer**
  - Objectives:
    - To help clinicians with the management of patient data and images
    - To support primary breast cancer therapeutical decision
  - A web-based platform with 3 decision-support modules:
    - Clinical practice guidelines implementation using formal ontologies
    - Statistical machine learning through rule-learning
    - Case-based reasoning (CBR)

Introduction

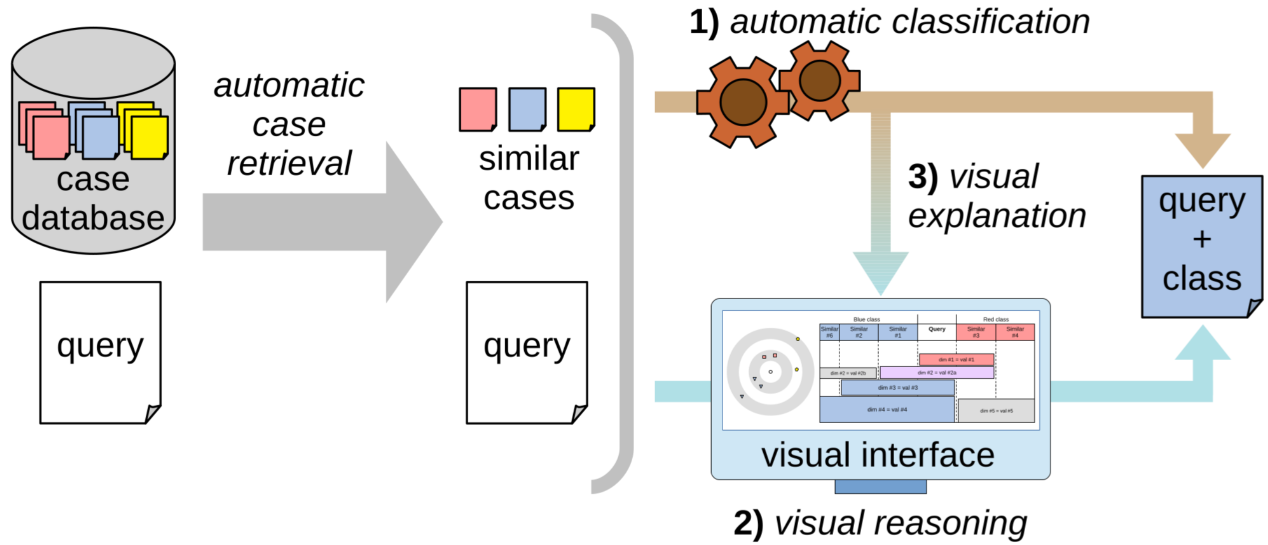
- **Case-based Reasoning (CBR)**
  - A form of analogical reasoning
    - No learning: CBR does not try to learn a model
    - Typical example: kNN (k nearest neighbor)
  - 3 steps:
    - Retrieve similar older cases from a database, including cases with known solutions
    - Adapt their solutions to the new case
    - Retain the new case in the case database
  - In the therapeutic context
    - A case = a patient
    - A solution = a treatment



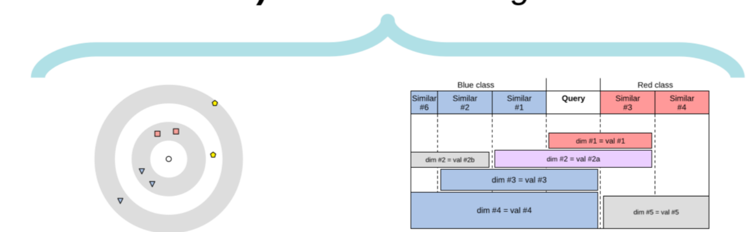
Introduction

- **Case-based Reasoning (CBR)**
  - Particularly interesting for producing explanations (XAI)
  - The old cases can be used as explanations
    - This way of reasoning is familiar to physicians
- **=> Explanations may consist is the presentation of 2-50 similar cases**
  - But 2-50 breast cancer patient records represent a huge volume of data!
  - A solution is the use of **information visualization** for displaying the cases

An automatic/visual approach to CBR



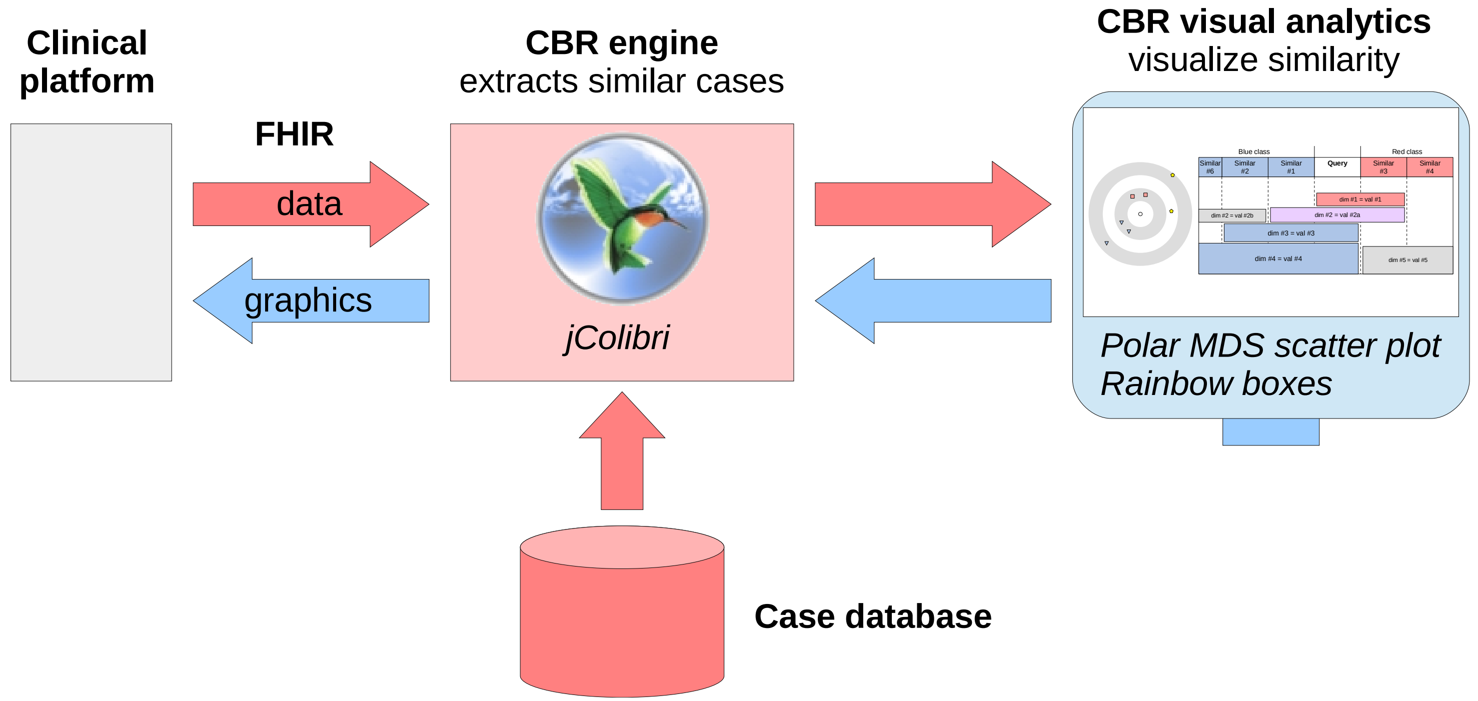
- **Previous works**
  - An be automatic or visual
    - Translate visually the CBR reasoning
  - Displays case similarities (new case vs old ones)
  - Qualitative similarity
  - Quantitative similarity



[Lamy JB *et al.* Explainable artificial intelligence for breast cancer: a visual case-based reasoning approach. Artificial Intelligence in Medicine 2019]

Architecture

- Case database is a relational database
- HL7 FHIR standard is used for communication with the clinical platform
- Cases are retrieved using jColibri



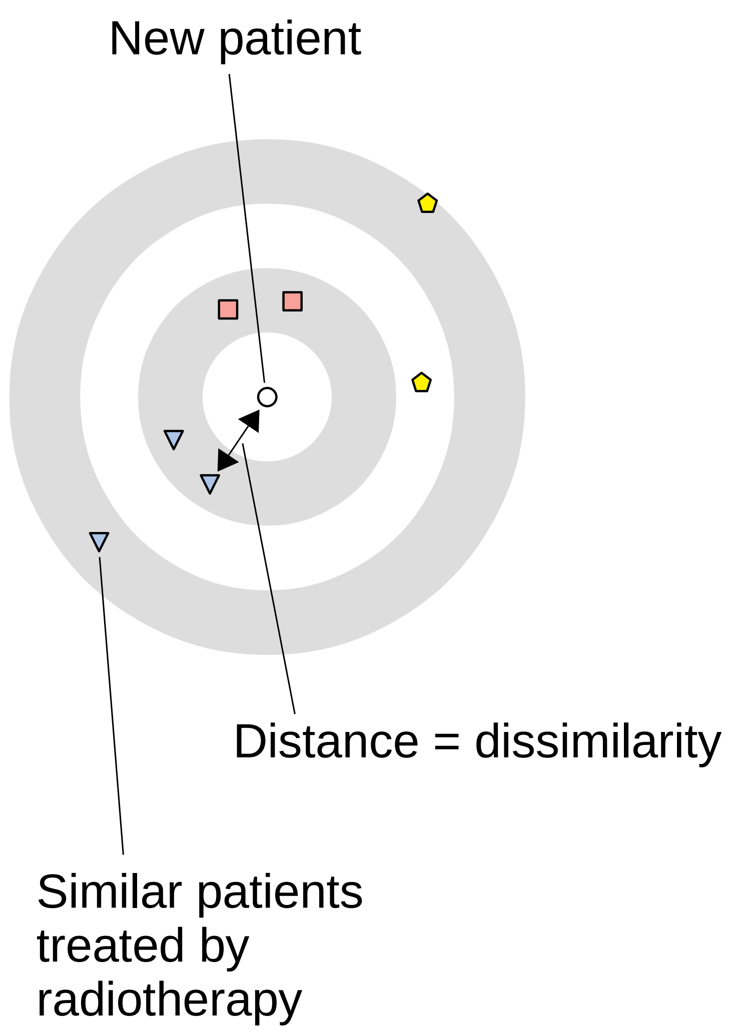
Distance matrix

- **Cases are retrieved using jColibri**
  - Computes a distance matrix between cases

	Query	Similar #1	Similar #2	Similar #3	Similar #4	Similar #5	Similar #6	Similar #7
dim #1	**val #1**	val #1b	val #1c	**val #1**	val #1d	val #1e	val #1f	val #1g
dim #2	**val #2a**	**val #2a**	**val #2b**	**val #2a**	val #2d	val #2e	**val #2b**	val #2g
dim #3	**val #3**	**val #3**	**val #3**	val #3c	val #3d	val #3e	val #3f	val #3g
dim #4	**val #4**	**val #4**	**val #4**	val #4c	val #4d	val #4e	**val #4**	val #4g
dim #5	val #5a	val #5b	val #5c	**val #5**	**val #5**	val #5e	val #5f	val #5g
dim #6	val #6	val #6a	val #6b	val #6c	val #6d	val #6e	val #6f	val #6g
...								

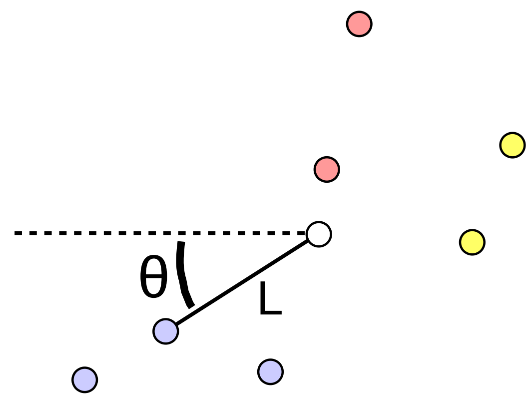
	Query	Similar #1	Similar #2	Similar #3	Similar #4	Similar #5	Similar #6	Similar #7
Query	-							
Similar #1	2.0	-						
Similar #2	2.1	1.5	-					
Similar #3	2.0	5.0	4.8	-				
Similar #4	1.9	5.1	4.9	1.1	-			
Similar #5	4.5	5.2	5.2	6.0	6.1	-		
Similar #6	4,2	1.7	1.8	5.5	5.6	5.5	-	
Similar #7	2.0	5.3	5.1	5.4	5.3	3.1	5.2	-

Visualization of quantitative similarities



- **Scatter plot : 2D projection of the distance matrix**
  - 1 dot = 1 patient
  - Colors = classes
  - Target facilitates distance evaluation
- **Various methods for scatter plot**
  - MDS 5multi-Dimensional Scaling), PCA, tSNE,...
- **Here, 2 types of distances:**
  - A - Between the new patient and a similar patient (more important!)
  - B - Between two similar patients
- **=> we used polar MDS**
  - Preserve distances of type A to the detriment of those of type B

Polar MDS scatter plot



- Origin O = new patient
- Each similar case S is defined by their polar coordinates (L, θ)
- L is already known: it is the distance between S and O
- θ is determined by solving an optimization problem:
  - Find the best values θ that minimize the stress function:

$$S_p(d) = \sum_{2<i<j} \frac{(d_{ij} - \delta_{ij})^2}{d_{ij}}$$

2-dimensional distance
in the scatter plot
(depend on θ values)

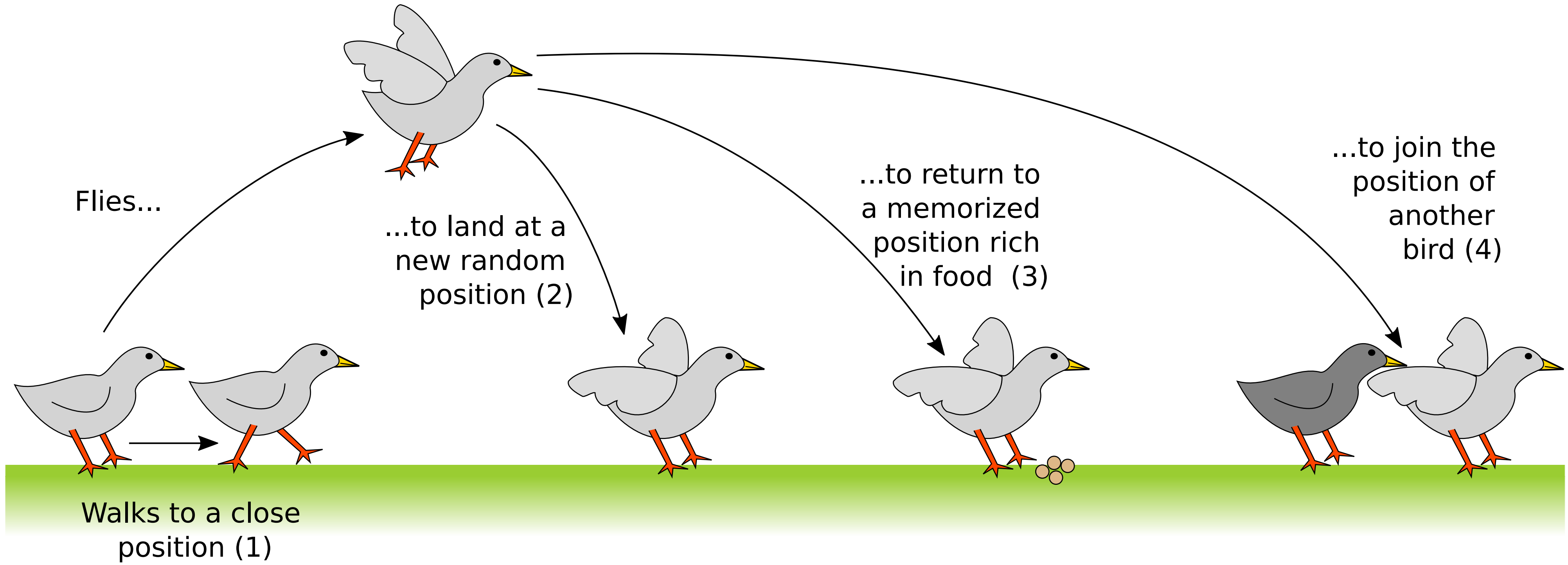
Real n-dimensional distance

Number 1 is the new patient

=> no information loss for the distances involving the new patient

AFB metaheuristic

Artificial Feeding Birds (AFB)
[Lamy JB. Artificial Feeding Birds (AFB): a new metaheuristic inspired by the behavior of pigeons, Advances in nature-inspired computing and applications 2019, Springer]



- **Simple**
- **Performant**
- **Generic**

Can solve any optimisation problem defined by a triplet of functions (*cost*(), *fly*(), *walk*())

Visualization of qualitative similarities

- **Rainbow boxes**
  - A recent set visualization technique
  - Elements are patients
  - Sets are shared characteristics
    - set of patients with “age > 60”
  - Only the two major therapeutic decisions are kept
  - Numeric values are discretized using the Minimum Description Length Principle (MDLP)
  - Only the boxes with the highest Mutual Information (MI) are kept

1)

	Query	Similar #1	Similar #2	Similar #3	Similar #4	Similar #5	Similar #6	Similar #7
dim #1	**val #1**	val #1b	val #1c	**val #1**	val #1d	val #1e	val #1f	val #1g
dim #2	**val #2a**	**val #2a**	**val #2b**	**val #2a**	val #2d	val #2e	**val #2b**	val #2g
dim #3	**val #3**	**val #3**	**val #3**	val #3c	val #3d	val #3e	val #3f	val #3g
dim #4	**val #4**	**val #4**	**val #4**	val #4c	val #4d	val #4e	**val #4**	val #4g
dim #5	val #5a	val #5b	val #5c	**val #5**	**val #5**	val #5e	val #5f	val #5g
dim #6	val #6	val #6a	val #6b	val #6c	val #6d	val #6e	val #6f	val #6g
…								

2)

	Similar #6	Similar #2	Similar #1	Query	Similar #3	Similar #4
dim #1	val #1f	val #1c	val #1b	**val #1**	**val #1**	val #1d
dim #2	**val #2b**	**val #2b**	**val #2a**	**val #2a**	**val #2a**	val #2d
dim #3	val #3f	**val #3**	**val #3**	**val #3**	val #3c	val #3d
dim #4	**val #4**	**val #4**	**val #4**	**val #4**	val #4c	val #4d
dim #5	val #5f	val #5c	val #5b	val #5a	**val #5**	**val #5**
dim #6	val #6f	val #6b	val #6a	val #6	val #6c	val #6d
…						

3)

<table>
<tr><th></th><th>Similar #6</th><th>Similar #2</th><th>Similar #1</th><th>Query</th><th>Similar #3</th><th>Similar #4</th></tr>
<tr><td>dim #1</td><td>val #1f</td><td>val #1c</td><td>val #1b</td><td colspan="2">dim #1 = val #1</td><td>val #1d</td></tr>
<tr><td>dim #2</td><td colspan="2">dim #2 = val #2b</td><td colspan="3">dim #2 = val #2a</td><td>val #2d</td></tr>
<tr><td>dim #3</td><td>val #3f</td><td colspan="3">dim #3 = val #3</td><td>val #3c</td><td>val #3d</td></tr>
<tr><td>dim #4</td><td colspan="4">dim #4 = val #4</td><td>val #4c</td><td>val #4d</td></tr>
<tr><td>dim #5</td><td>val #5f</td><td>val #5c</td><td>val #5b</td><td>val #5a</td><td colspan="2">dim #5 = val #5</td></tr>
<tr><td>dim #6</td><td>val #6f</td><td>val #6b</td><td>val #6a</td><td>val #6</td><td>val #6c</td><td>val #6d</td></tr>
<tr><td>…</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
</table>

4)

<table>
<tr><th>Similar #6</th><th>Similar #2</th><th>Similar #1</th><th>Query</th><th>Similar #3</th><th>Similar #4</th></tr>
<tr><td></td><td></td><td></td><td colspan="2">dim #1 = val #1</td><td></td></tr>
<tr><td colspan="2">dim #2 = val #2b</td><td colspan="3">dim #2 = val #2a</td><td></td></tr>
<tr><td></td><td colspan="3">dim #3 = val #3</td><td></td><td></td></tr>
<tr><td colspan="4">dim #4 = val #4</td><td colspan="2">dim #5 = val #5</td></tr>
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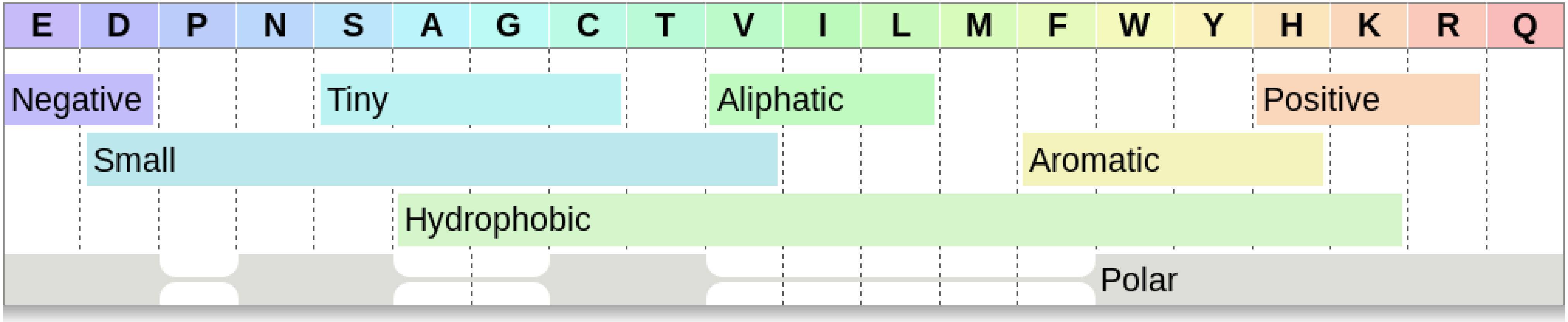
Rainbow boxes



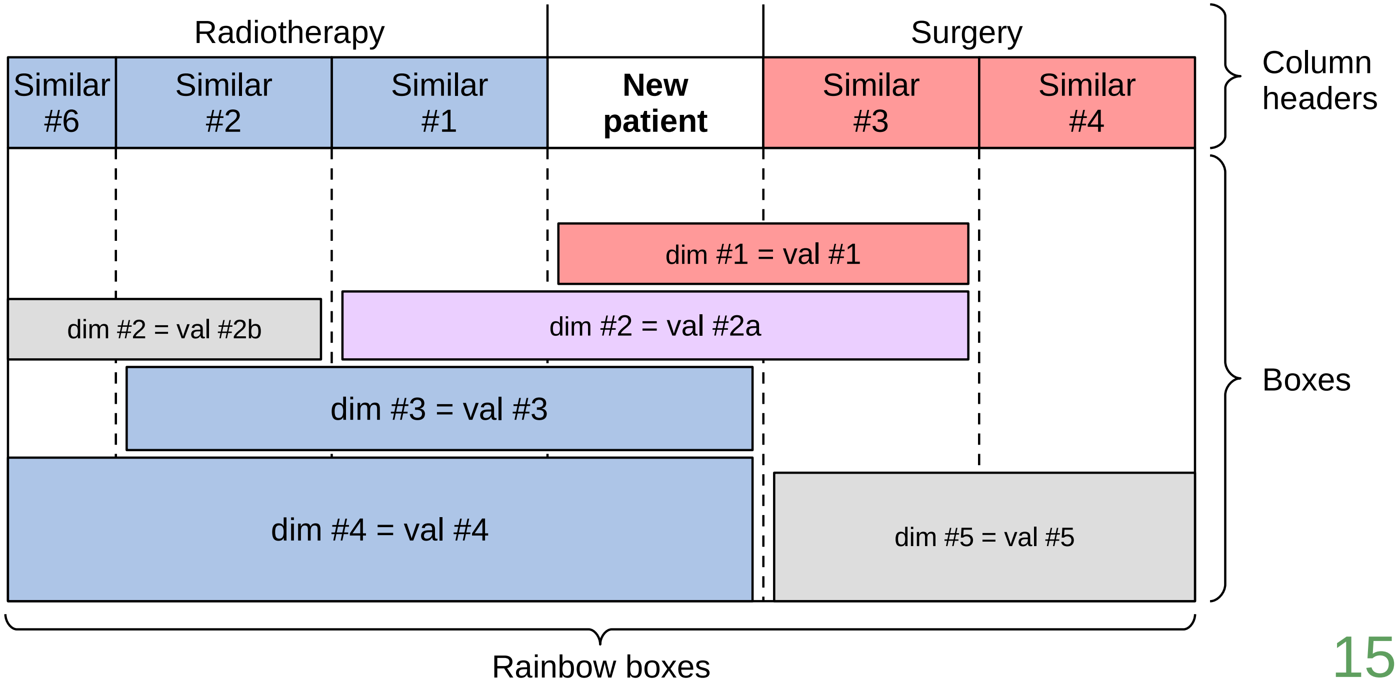
- **Rainbow boxes : a recent technique for set visualization**
  - elements => columns
  - sets => rectangular boxes
  - color => one color per element
  - box color is the mean of its elements color
  - non continguous element in a set => box hole
  - elements are ordered so as to minimize the number of holes
  - box are stacked vertically by size

[Lamy JB et al. Rainbow boxes: a new technique for overlapping set visualization and two applications in the biomedical domain. **Journal of Visual Language and Computing** 2017]

Rainbow boxes for patient similarity

- Column height = similarity with the new patient
- Box height = importance of the box (MI)
- Box color = weighted mean of the header's color
  - Indicate toward which therapy orientates the box

- Visual reasoning



Algorithmic translation of the visual reasoning

function classify(q, X, s, n, m):

q is the query case
X is the case database (we assume that $q \in X$)
s is the dissimilarity measure (a function taking 2 cases and returning their dissimilarity, *e.g.* Euclidean distance)
$n \geq 2$ is the total number of cases considered (query + similar cases)
$m \geq 1$ is the maximum number of boxes selected

For each case i in X, compute $s(q, X_i)$
Let X' be the set of selected cases, X' contains the n elements of X with the lowest dissimilarity $s(q, i)$
We assume that $X'_1 = q$ and X'_2 to X'_n are the similar cases

Let d be the distance matrix between cases in X'
For each case i in X':
  For each case j in X':
    $d_{i,j} = s(i, j)$

Let w be the weights of the similar cases

$$w_i = \begin{cases} 1 & \text{, if } s_{max} = s_{min} \\ \frac{s_{max} - s(q, X'_i)}{s_{max} - s_{min}} & \text{, otherwise} \end{cases}$$

with $s_{min} = \min(s(q, X'_i))$ and $s_{max} = \max(s(q, X'_i))$

Let y_1 and y_2 be the two best classes in X' (determined by a majority vote over similar cases, weighted by w_i)
Let X'' be the subset of X' displayed in rainbow boxes
$X'' = X' \cap (\{q\} \cup y_1 \cup y_2)$

Let B be the set of candidates boxes (currently empty)
For each dimension Z:
  If Z has numeric values:
    Discretize Z
  For each value v that Z takes in cases X'':
    If q has value v for dimension Z:
      Add $Zv = \{x \in X'' \mid x_Z = v\}$ **into** B

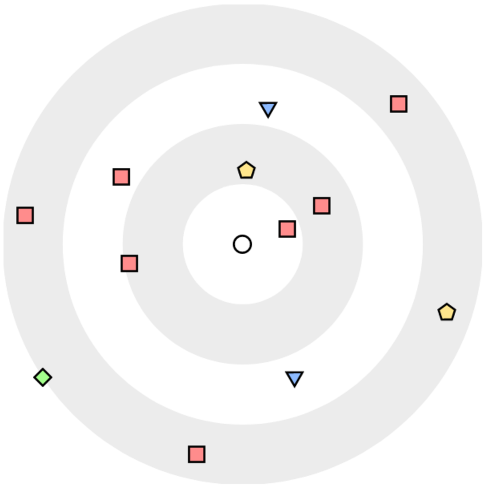
For each box Zv in B, compute $MI(Z_vY) = \sum_{z \in \{Z=v, Z \neq v\}} \sum_{y \in \{y_1, y_2\}} p(z, y) \log\left(\frac{p(z,y)}{p(z)p(y)}\right)$

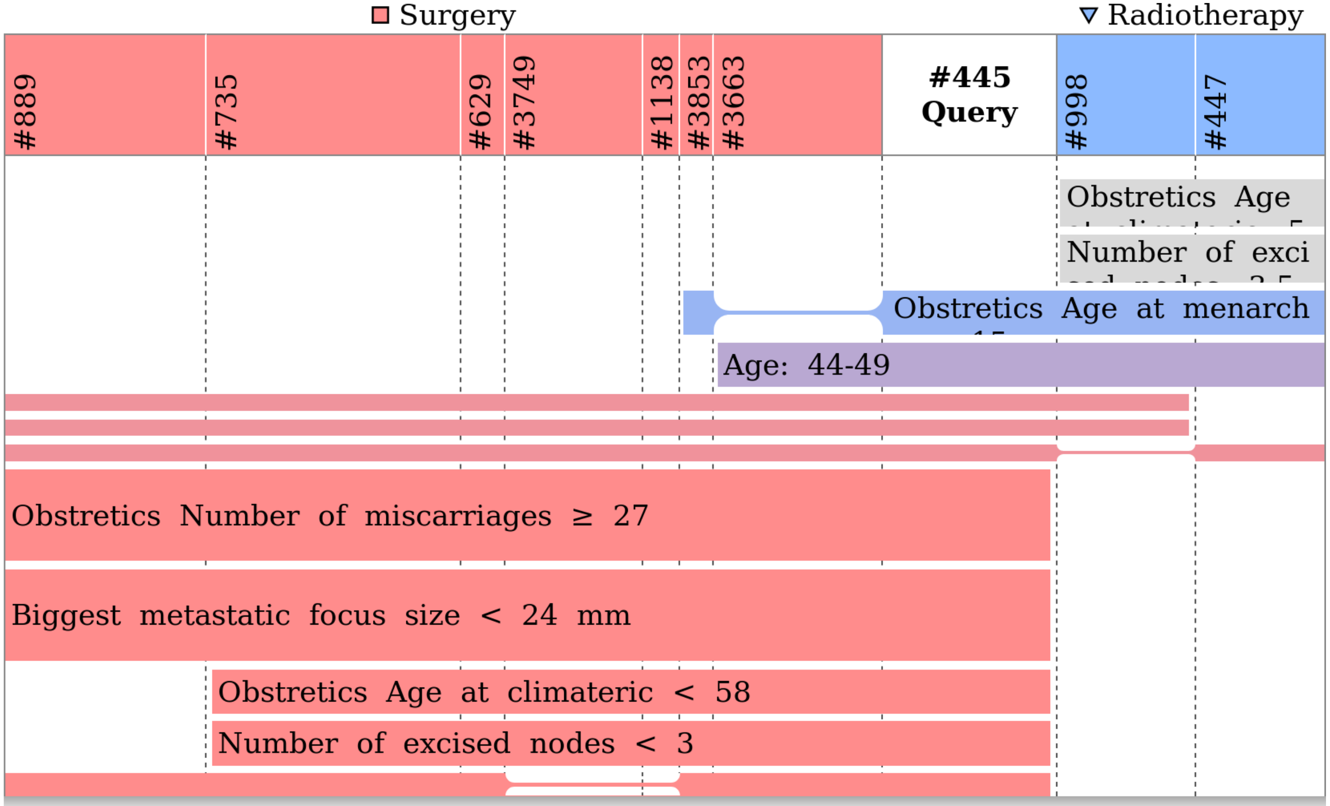
with $p(y) = \frac{|y|}{|X'' \setminus \{q\}|}$, $p(Z = v) = \frac{|Z_v|}{|X'' \setminus \{q\}|}$, $p(Z \neq v) = \frac{|X'' \setminus Z_v|}{|X'' \setminus \{q\}|}$, $p(Z = v, y) = \frac{|Z_v \cap y|}{|X'' \setminus \{q\}|}$, $p(Z \neq v, y) = \frac{|(X'' \setminus Z_v) \cap y|}{|X'' \setminus \{q\}|}$
Let B' be the set of selected boxes, B' contains the m elements of B with the highest $MI(Z_vY)$

Compute $S_{y_1} = \sum_{Z_v \in B'} \left(MI(Z_vY) \times \sum \{w_{2 \leq i \leq n} \mid x_i \in Z_v \cap y_1\}\right)$
Compute $S_{y_1} = \sum_{Z_v \in B'} \left(MI(Z_vY) \times \sum \{w_{2 \leq i \leq n} \mid x_i \in Z_v \cap y_2\}\right)$

If $S_{y_1} > S_{y_2}$:
  return y_1
Else:
  return y_2

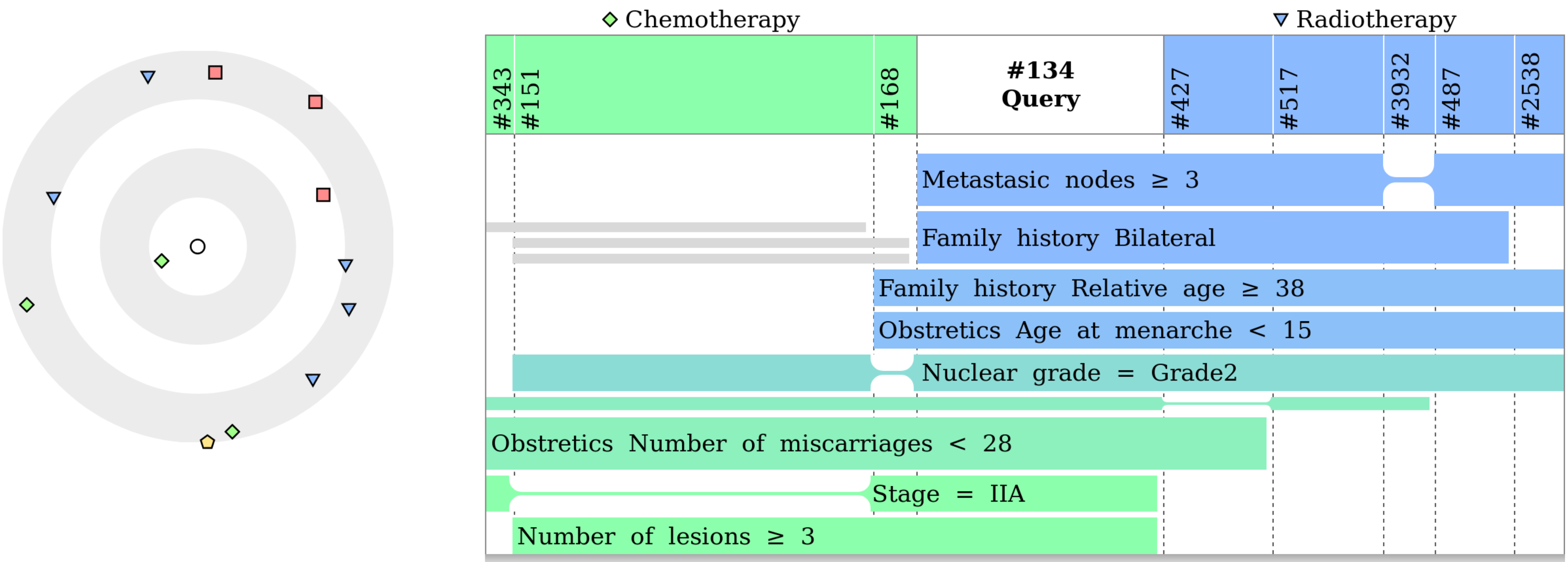
Resulting interface





- Boxes give arguments in favor one type of therapy
- Physicians may choose a different option if he disagrees

Resulting interface

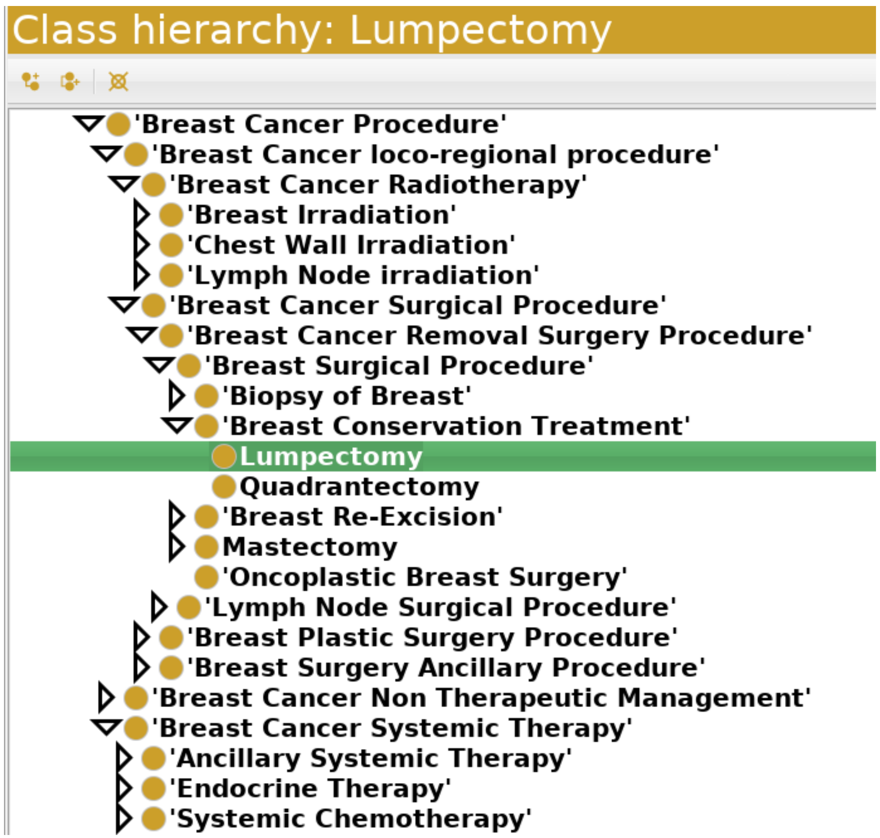


- Boxes give arguments in favor one type of therapy
- Physicians may choose a different option if he disagrees

- Limited to 2-6 classes of therapy
- => Hierarchical approach dividing the decision in several smaller ones

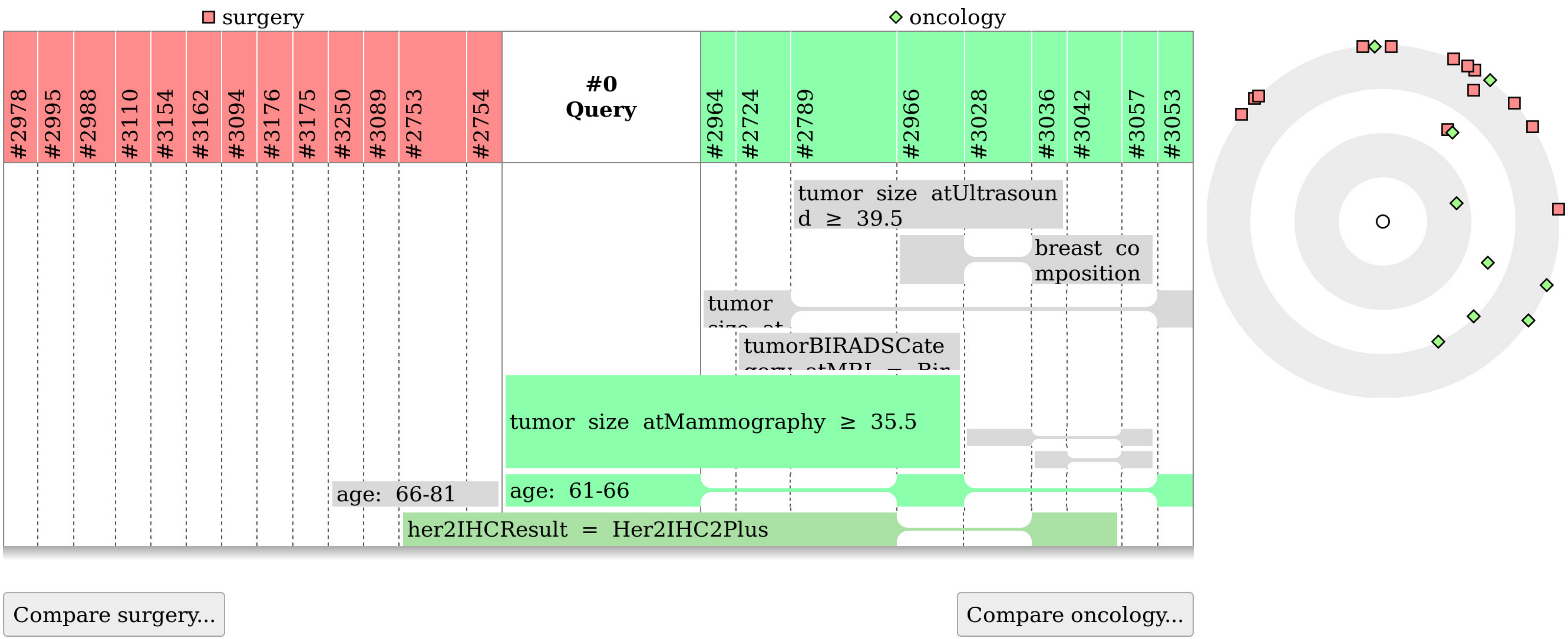
Ontology of breast cancer therapy

- **We organized possible therapies in a formal ontology**
  - OWL format
  - Owlready ontology-oriented programming module for Python

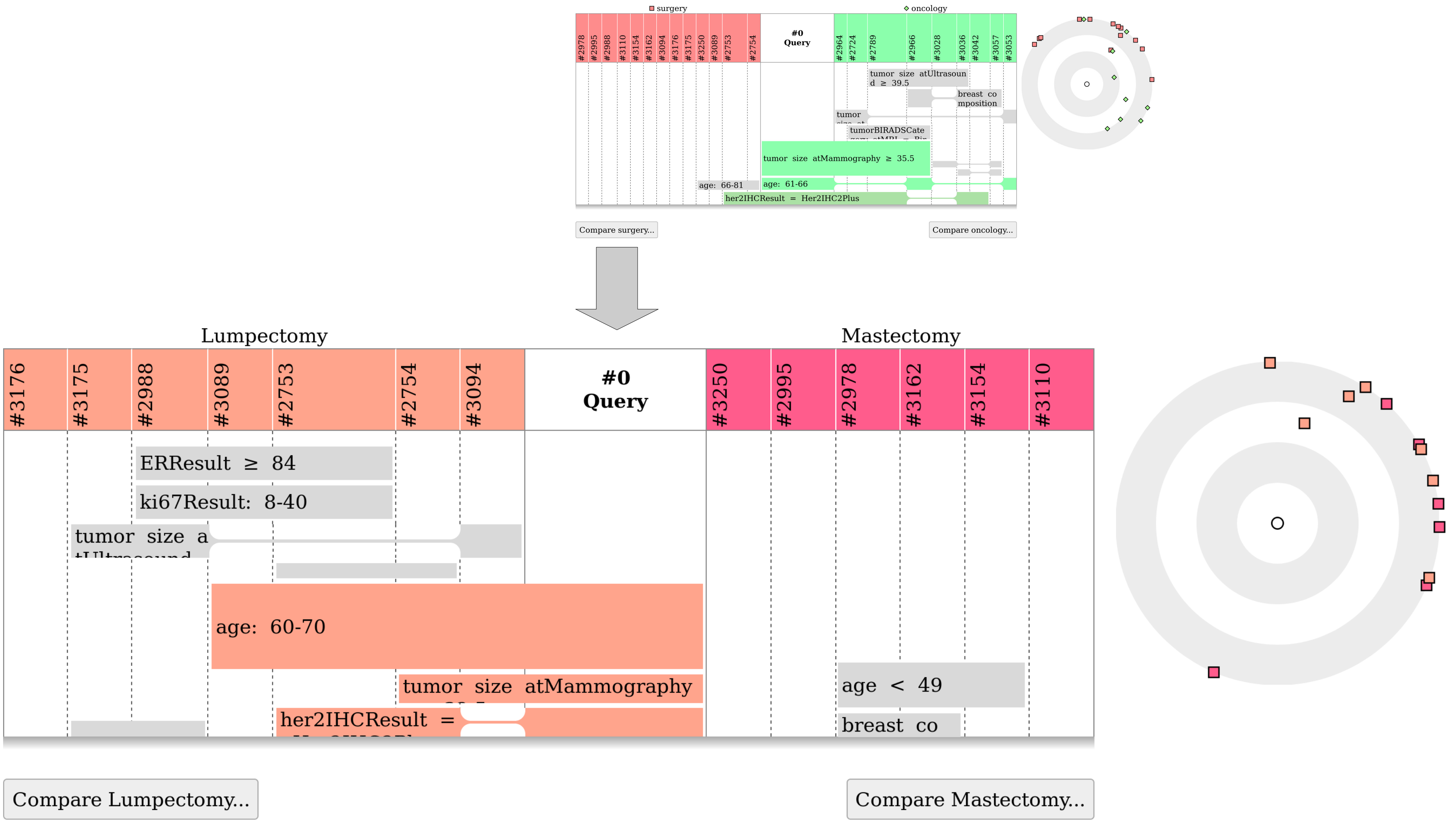


French book on Owlready!
JB Lamy
Python et les ontologies
ENI editions, 2019

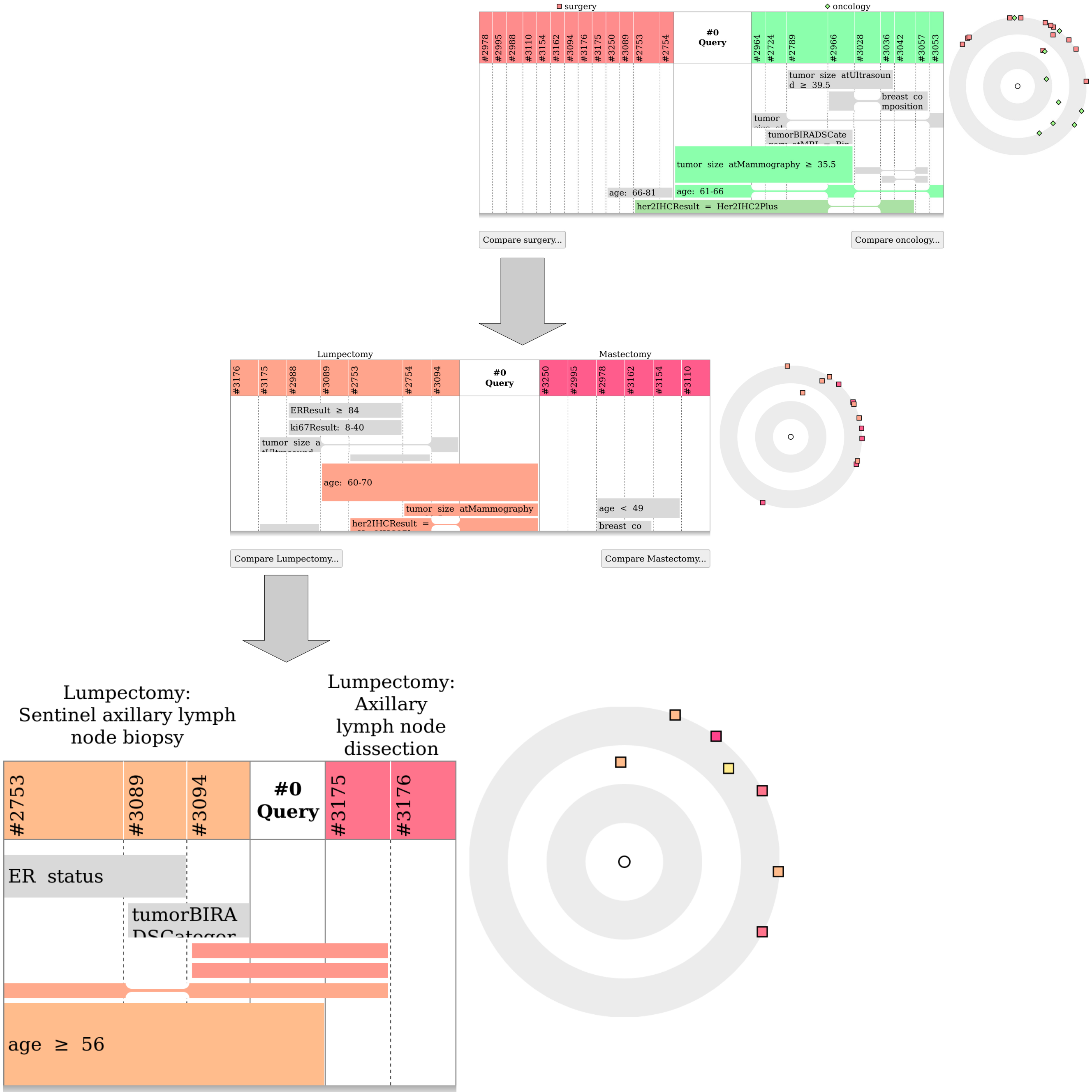
Hierarchical approach



- Buttons allow to choose one of the two major classes of therapy
- Then, the visualization is limited to the similar patients with this therapy
- New classes are determined, according to the ontology



surgery
oncology
#2978 #2995 #2988 #3110 #3154 #3162 #3094 #3176 #3175 #3250 #3089 #2753 #2754
#0
Query
#2964 #2724 #2789 #2966 #3028 #3036 #3042 #3057 #3053
tumor size atUltrasound ≥ 39.5
breast composition
tumorBIRADSCate
tumor size atMammography ≥ 35.5
age: 66-81
age: 61-66
her2IHCResult = Her2IHC2Plus
Compare surgery...
Compare oncology...
Lumpectomy
Mastectomy
#3176 #3175 #2988 #3089 #2753 #2754 #3094
#0
Query
#3250 #2995 #2978 #3162 #3154 #3110
ERResult ≥ 84
ki67Result: 8-40
tumor size a
age: 60-70
tumor size atMammography
her2IHCResult =
age < 49
breast co
Compare Lumpectomy...
Compare Mastectomy...


surgery
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#3057
#3053
tumor size atUltrasound ≥ 39.5
breast composition
tumor
tumorBIRADSCate
tumor size atMammography ≥ 35.5
age: 66-81
age: 61-66
her2IHCResult = Her2IHC2Plus
Compare surgery...
Compare oncology...
Lumpectomy
Mastectomy
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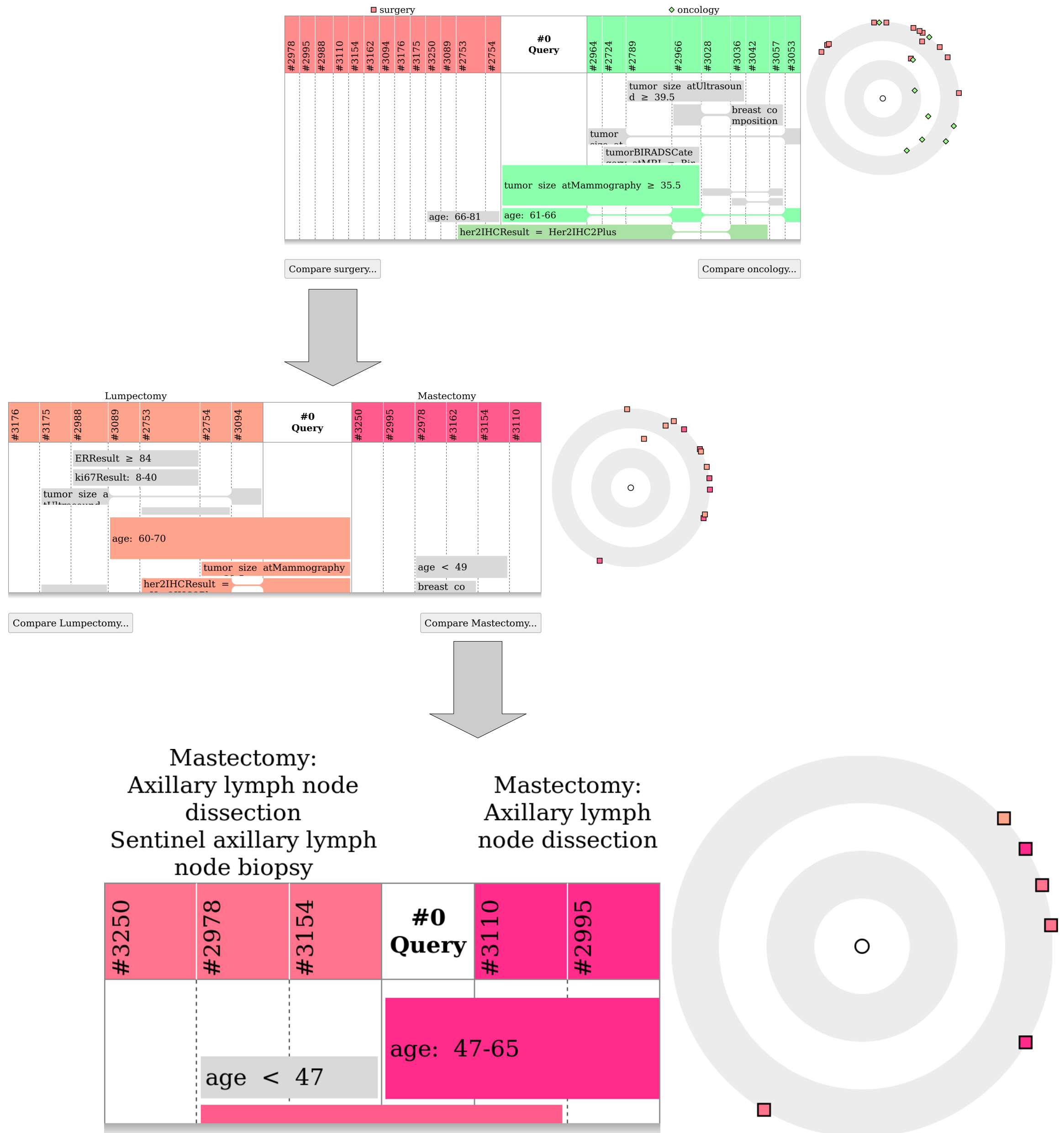
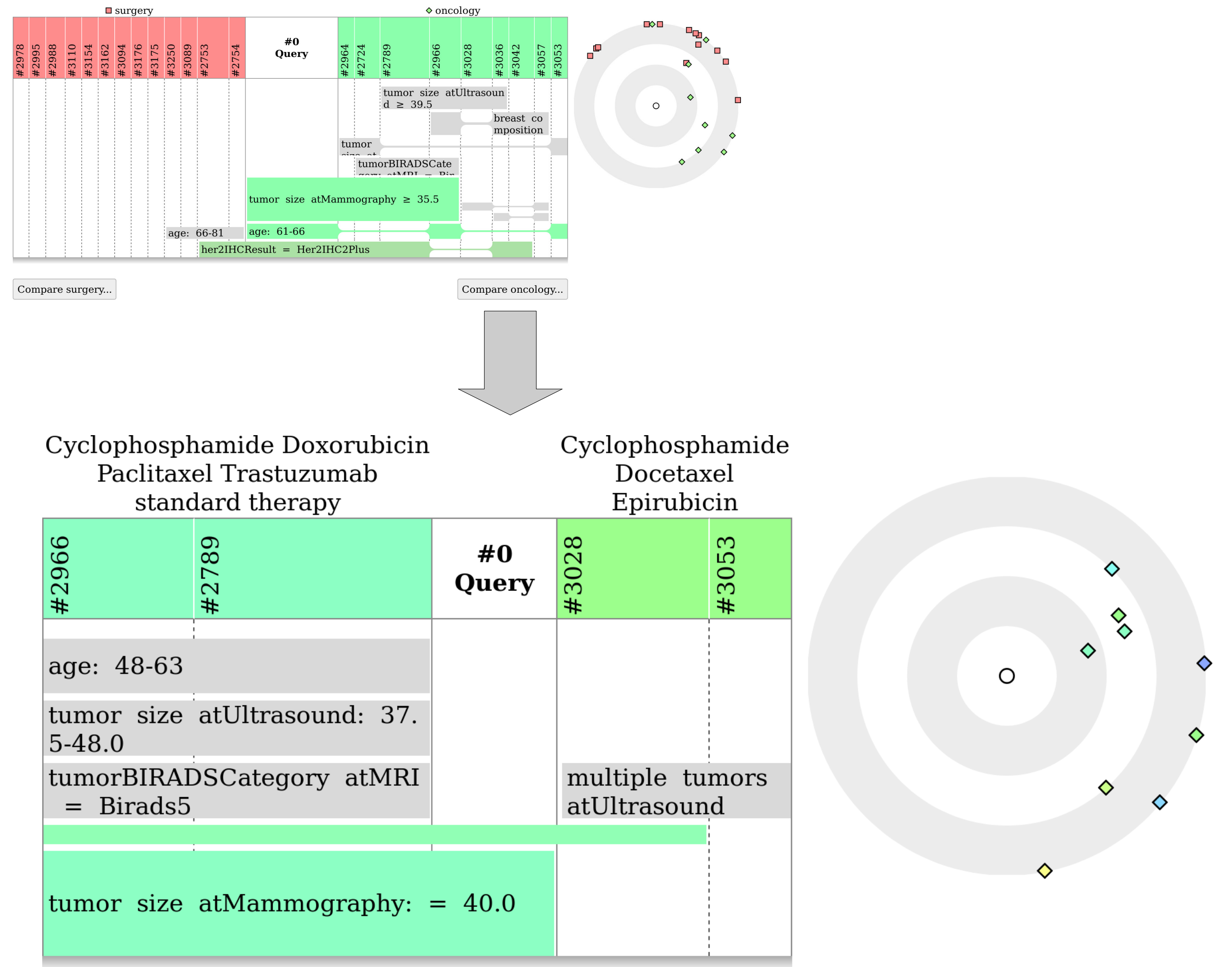
ERResult ≥ 84
ki67Result: 8-40
tumor size a
age: 60-70
tumor size atMammography
her2IHCResult =
age < 49
breast co
Compare Lumpectomy...
Compare Mastectomy...
Lumpectomy: Sentinel axillary lymph node biopsy
Lumpectomy: Axillary lymph node dissection
#2753
#3089
#3094
#0 Query
#3175
#3176
ER status
tumorBIRA
age ≥ 56


surgery
oncology
#2978 #2995 #2988 #3110 #3154 #3162 #3094 #3176 #3175 #3250 #3089 #2753 #2754
#0 Query
#2964 #2724 #2789 #2966 #3028 #3036 #3042 #3057 #3053
tumor size atUltrasound ≥ 39.5
breast composition
tumor
tumorBIRADSCategory
tumor size atMammography ≥ 35.5
age: 66-81
age: 61-66
her2IHCResult = Her2IHC2Plus
Compare surgery...
Compare oncology...
Lumpectomy
Mastectomy
#3176 #3175 #2988 #3089 #2753 #2754 #3094
#0 Query
#3250 #2995 #2978 #3162 #3154 #3110
ERResult ≥ 84
ki67Result: 8-40
age: 60-70
tumor size atMammography
her2IHCResult =
age < 49
breast co
Compare Lumpectomy...
Compare Mastectomy...
Mastectomy: Axillary lymph node dissection Sentinel axillary lymph node biopsy
Mastectomy: Axillary lymph node dissection
#3250 #2978 #3154
#0 Query
#3110 #2995
age < 47
age: 47-65



surgery
oncology
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#2988
#3110
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#3176
#3175
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#3089
#2753
#2754
#0 Query
#2964
#2724
#2789
#2966
#3028
#3036
#3042
#3057
#3053
tumor size atUltrasound ≥ 39.5
breast composition
tumorBIRADSCategory atMRI
tumor size atMammography ≥ 35.5
age: 66-81
age: 61-66
her2IHCResult = Her2IHC2Plus
Compare surgery...
Compare oncology...
Cyclophosphamide Doxorubicin Paclitaxel Trastuzumab standard therapy
Cyclophosphamide Docetaxel Epirubicin
#2966
#2789
#0 Query
#3028
#3053
age: 48-63
tumor size atUltrasound: 37.5-48.0
tumorBIRADSCategory atMRI = Birads5
multiple tumors atUltrasound
tumor size atMammography: = 40.0

Discussion and conclusion

- **A hierarchical visual approach for explainable therapeutical decision-making**
- **Similar accuracy as kNN, but better explainability**
- **Main limits:**
  - May require some training for the physicians
  - Number of similar cases is reduced at each iteration
    - Should we extract additional cases to compensate?
- **Set visualization is an interesting approach to explainable artificial intelligence (XAI)**
- **Perspectives:**
  - Clinical validation and evaluation
  - Adaptation to other domains
  - Extension to other AI techniques (deep learning, boosting)

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