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New Ways to Diagnose and Monitor CCA

Pedro M. Rodrigues & Juan Valle

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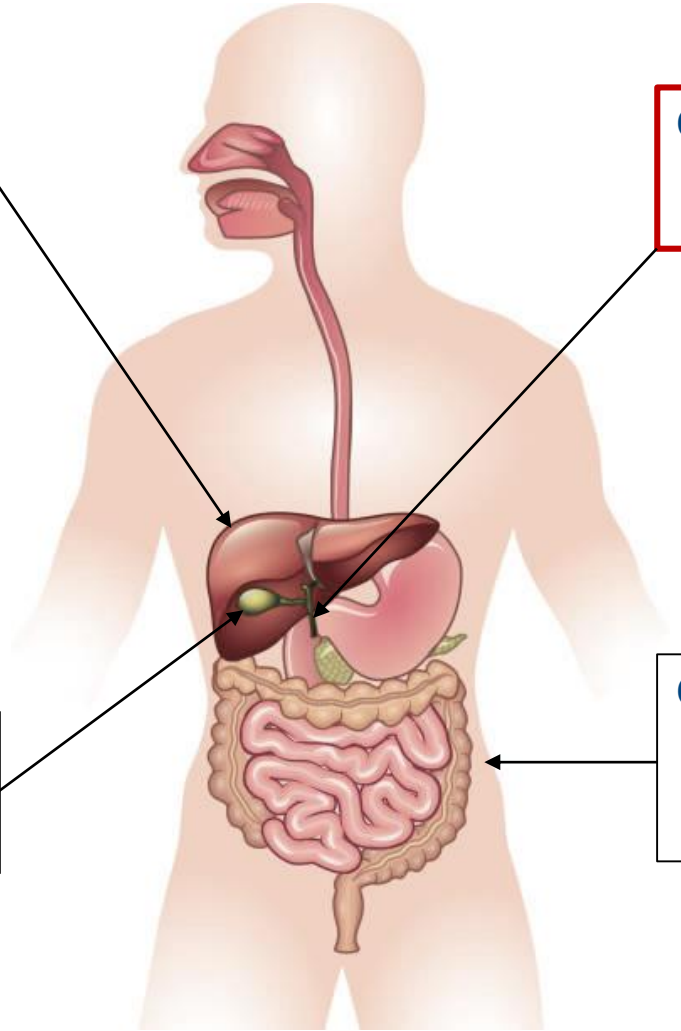
CONFERENCE

I have nothing to disclose

PSC and the risk of cancer

Hepatocellular carcinoma (HCC)
0.3%-2.8% lifetime incidence
>50 years and cirrhosis

Cholangiocarcinoma (CCA)
Up to 20% lifetime incidence
400x risk over general population



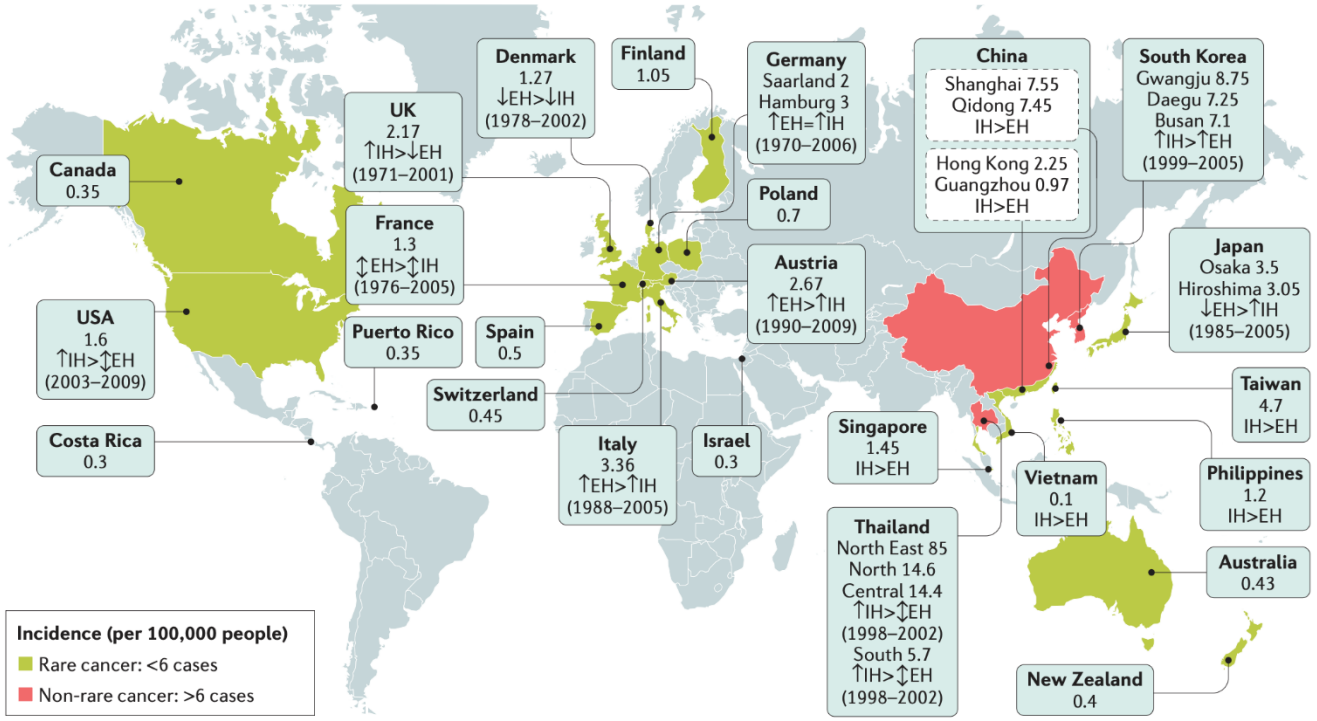
Gallblader carcinoma (GbC)
1%-3.5% lifetime incidence
10x risk over general population

Colorectal cancer (CRC)
20%-230% lifetime incidence in PSC-IBD
10x risk over general population
4x risk over patients with UC

Cholangiocarcinoma (CCA) general features

- **Heterogeneous** group of malignancies with features of biliary tract differentiation
- **Second** most common primary liver cancer; CCA incidence is increasing worldwide

Worldwide CCA incidence rates



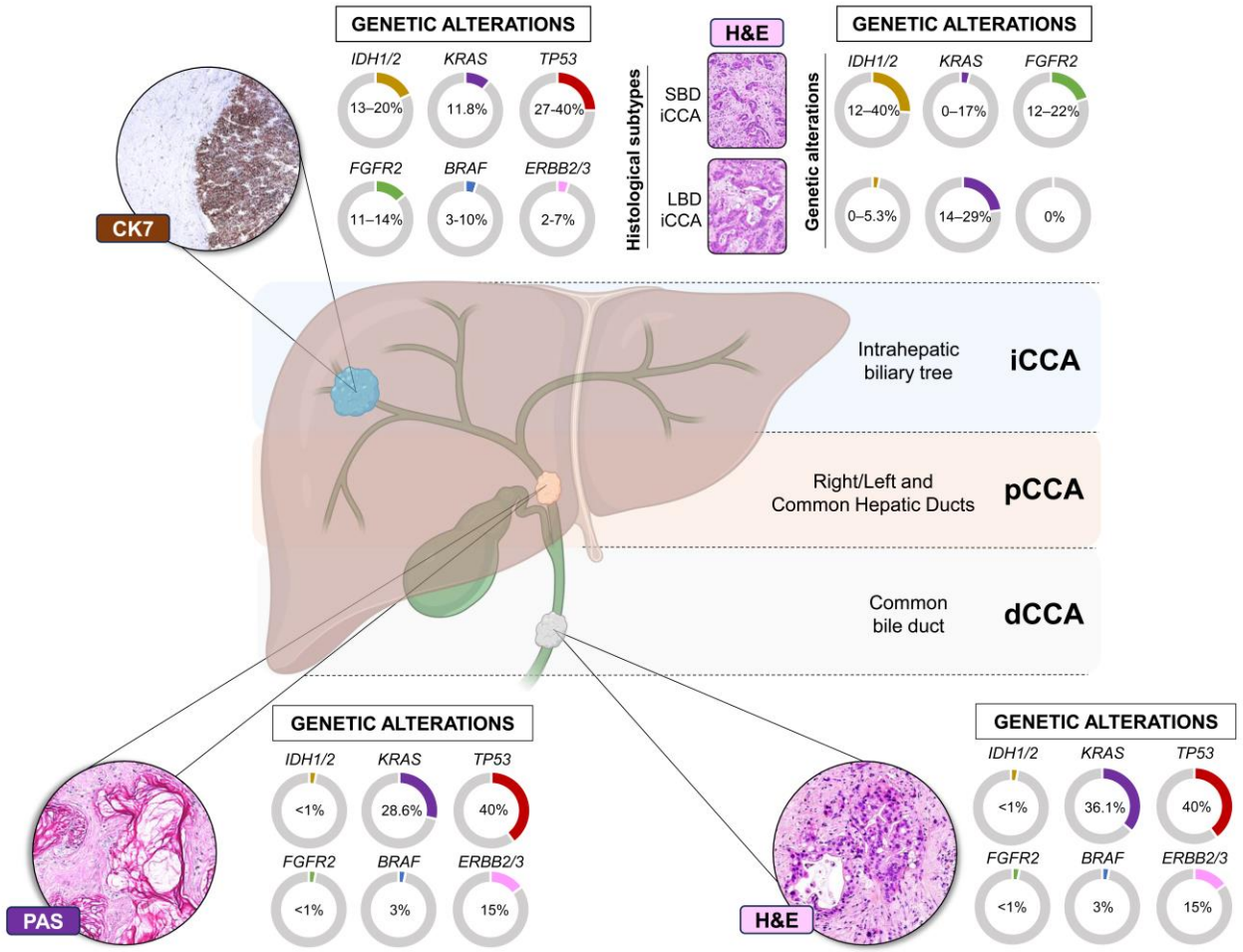
Eastern countries
(Thailand, China and S Korea: >6/100,000)

Western countries
(<4/100,000)

CCA, cholangiocarcinoma; EH, extrahepatic; IH, intrahepatic; S, South.

Banales JM, *et al. Nat Rev Gastroenterol Hepatol*. 2016

Cholangiocarcinoma (CCA) general features

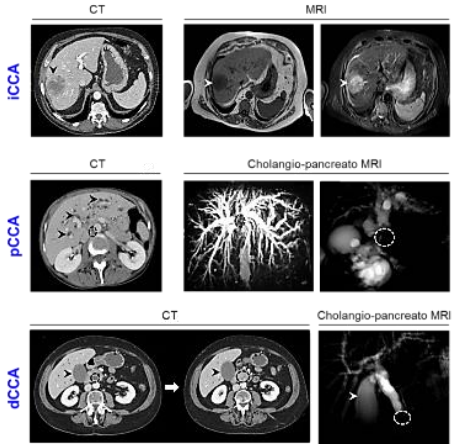


Banales JM, *et al. Nat Rev Gastroenterol Hepatol* 2025

Diagnosis of cholangiocarcinoma (CCA)

IMAGING

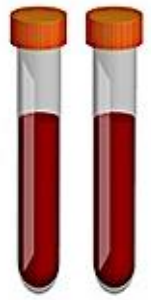
(CT, MRI, PET)



- NOT always accurate
- Difficult to differentiate malignant from benign strictures

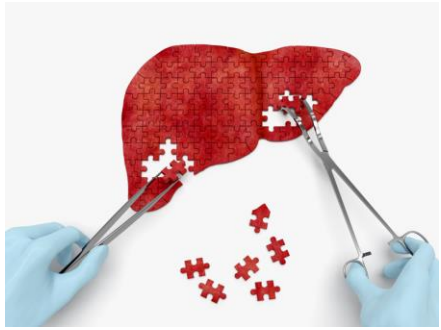
NON-SPECIFIC TUMOR MARKERS

(e.g., CA19-9)



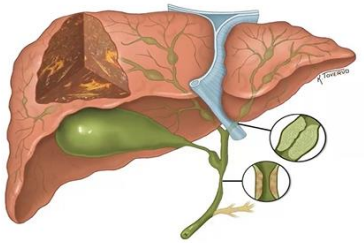
- **LOW** accuracy (SEN/SPE)
- ~10% unable to express
- Elevated in PSC
- Useless for early diagnosis

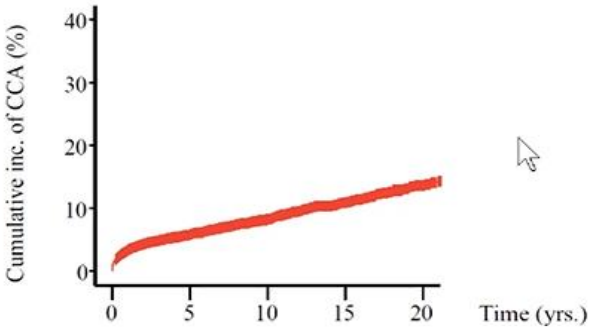
TUMOR BIOPSY/CYTOLOGY



- Accurate
- Invasive

PSC-CCA





- **Cumulative incidence** (20-years): **15%**[1]
- Median age: 40-50 years[1,2]
- **Note**: frequently arises in the **first year** of PSC diagnosis[1,3]

- **Difficult to diagnose** (overlapping symptoms & features between PSC and CCA)[3]

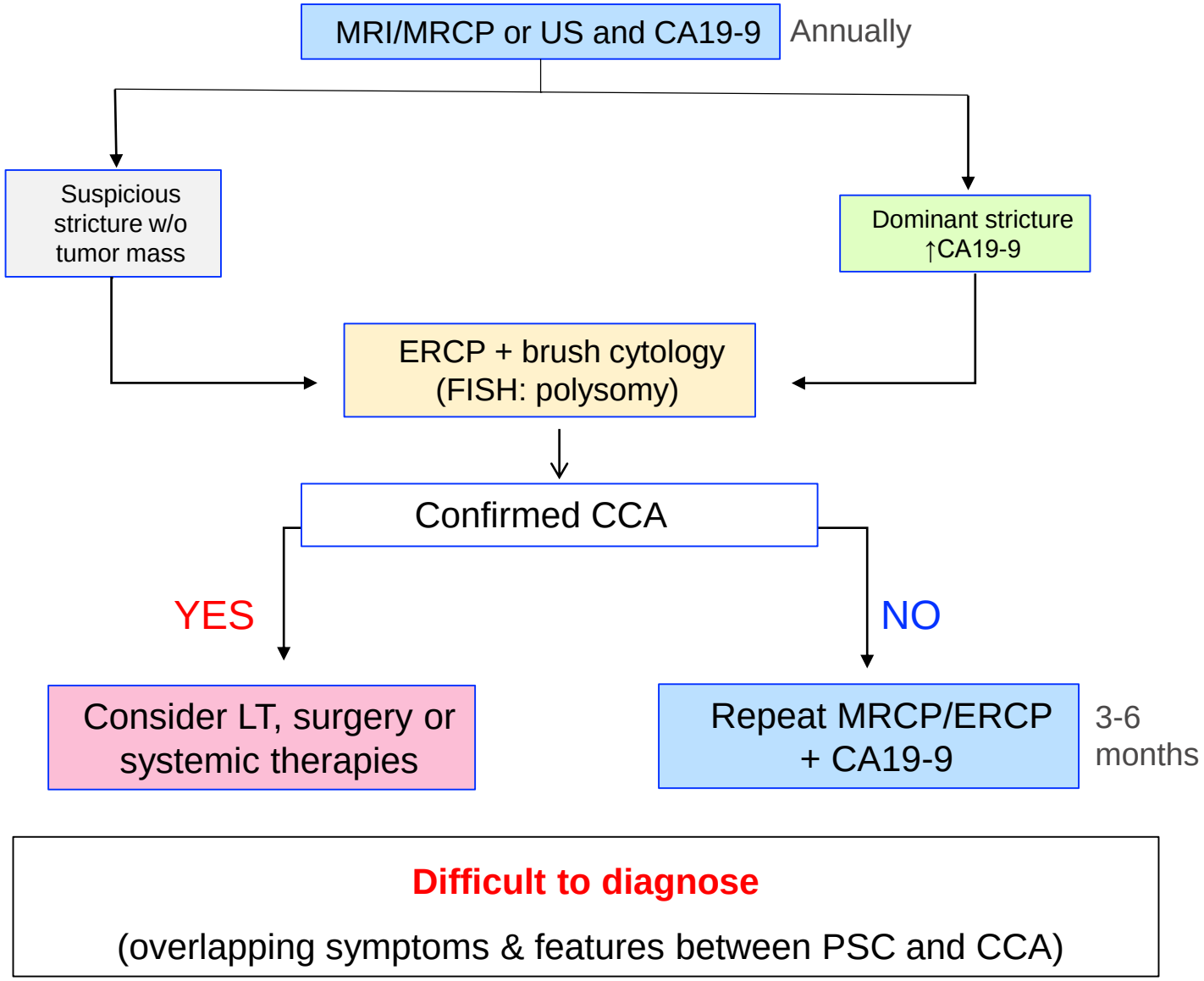
- **Surveillance:** 6-12 months by MRI/MRCP[4,5]

- **Dominant stricture, mass & ↑CA19.9:** ERCP + brush cytology (FIS: polysomy) [4,5]

- **Poor prognosis** (mOS: 5-12 months in unresectable cases)[3]
- Leading cause of **PSC-associated mortality** (24-58%)[2,3]

1. Weismueller T, *et al*. *Gastroenterology* 2017;152:1975-1984. 2. Boonstra K, *et al. Hepatology* 2013;58:2945-55.
3. Grimsrud MM, *et al*. *Liver International* 2019;39:2230-2237. 4. ESGE & EASL PSC Guidelines. J Hepatol 2017;66(6):1265-1281.
5. EASL PSC Guidelines. J Hepatol 2022;77(3):761-806.

PSC surveillance for early CCA detection

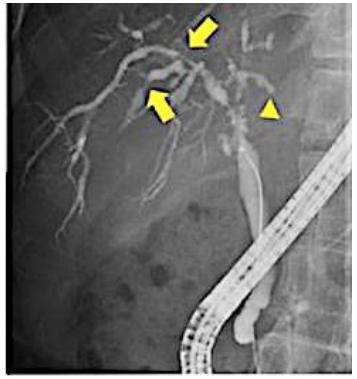


PSC-CCA diagnosis

PREDICTION

Is the patient going to develop CCA?

NON-INVAIVE DIAGNOSIS



Is that biliary stricture benign or malignant?

Accurate non-invasive biomarkers → Predict CCA development in PSC
Surveillance and early detection

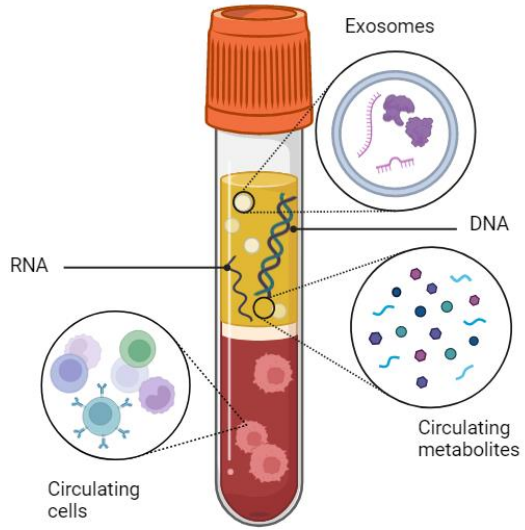
Liquid biopsy

- **Minimally invasive** approach for <u>biomarkers discovery</u>

Isolation and analysis of cell-derived material

(e.g., DNA, RNA, metabolites, EV…)

from **blood** or other **body fluids**

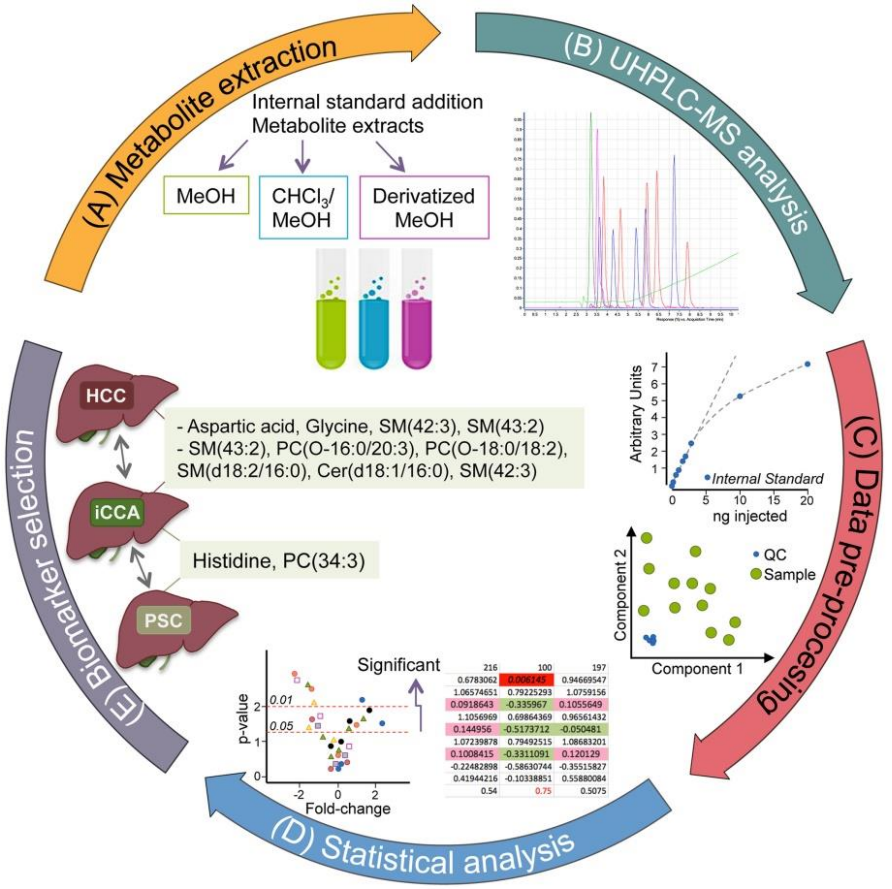


Serum metabolomics

Early and Differential diagnosis (**iCCA** and **HCC**)

250 μL serum

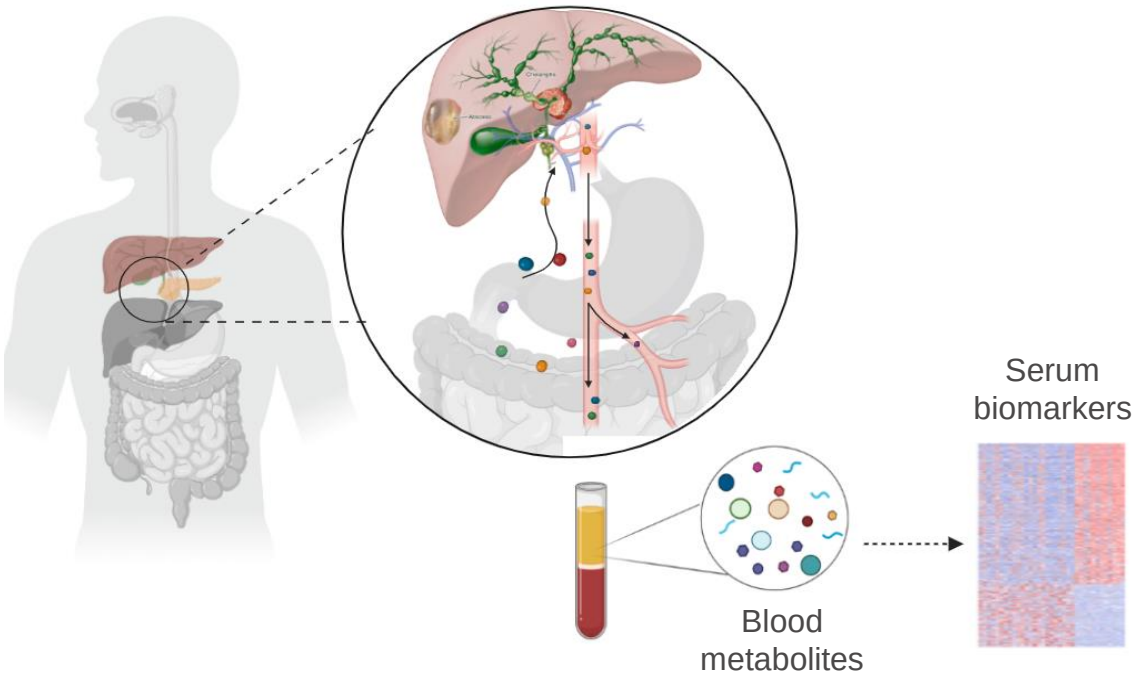
Diagnosis: **biopsy proven**



Banales JM, *et al. Hepatology* 2019;70(2):547-562.

Objective

Liquid biopsy metabolomics for
PSC and **PSC-CCA diagnosis**, and to **estimate CCA risk**

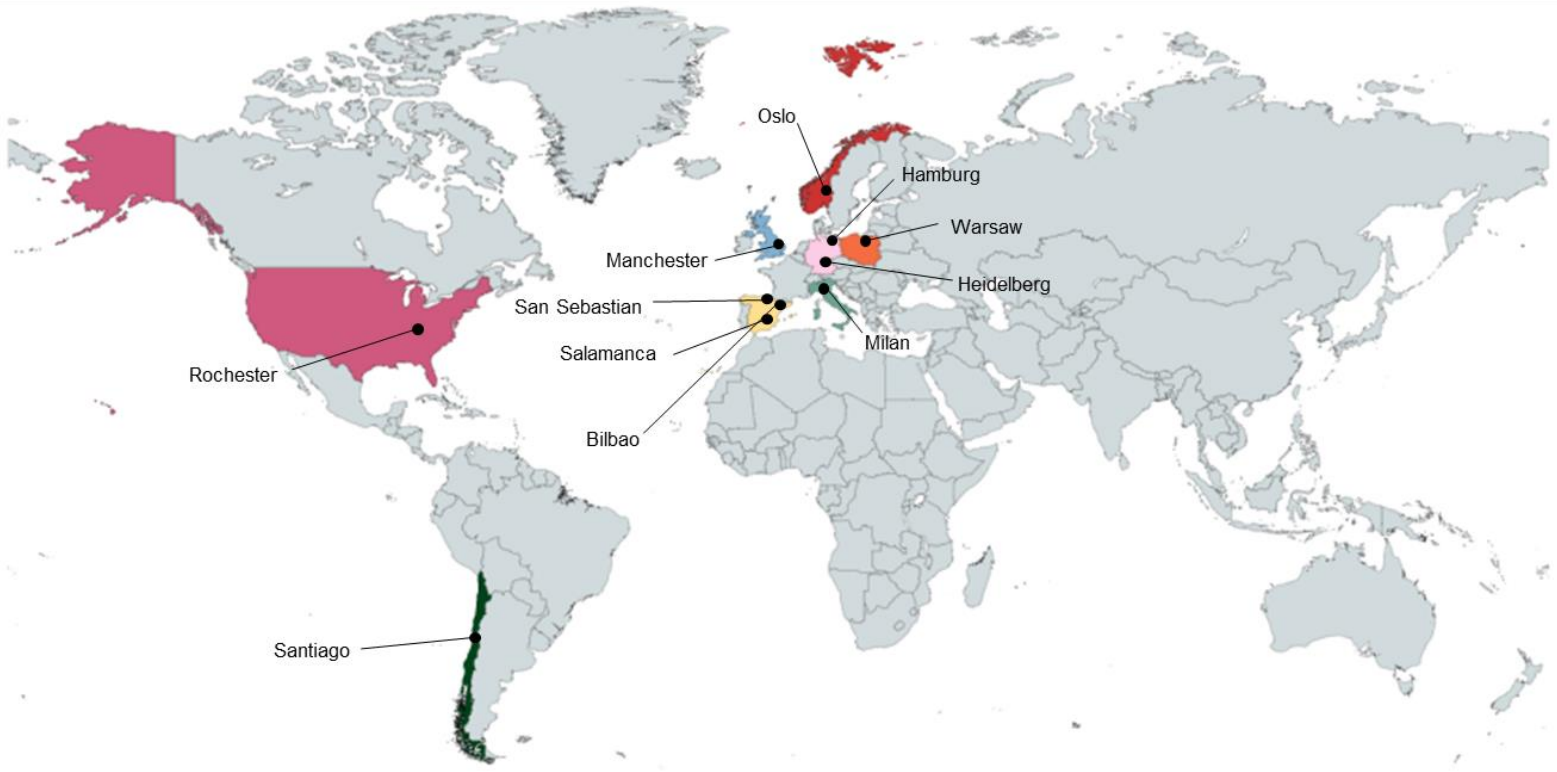


PSC diagnosis

PSC-CCA early diagnosis

Multicentre international study

13 Healthcare Centers from 8 countries



Collaborators

Tom Karlsen (Norway)
Trine Folseraas (Norway)
Johannes E.R. Hov (Norway)
Piotr Milkiewicz (Poland)
Marco Carbone (Italy)
Juan Valle/Angela Lamarca (UK)
Rocio Macias (Spain)
Domingo Balderramo (Argentina)
Marco Arrese (Chile)
Javier Bustamante (Spain)
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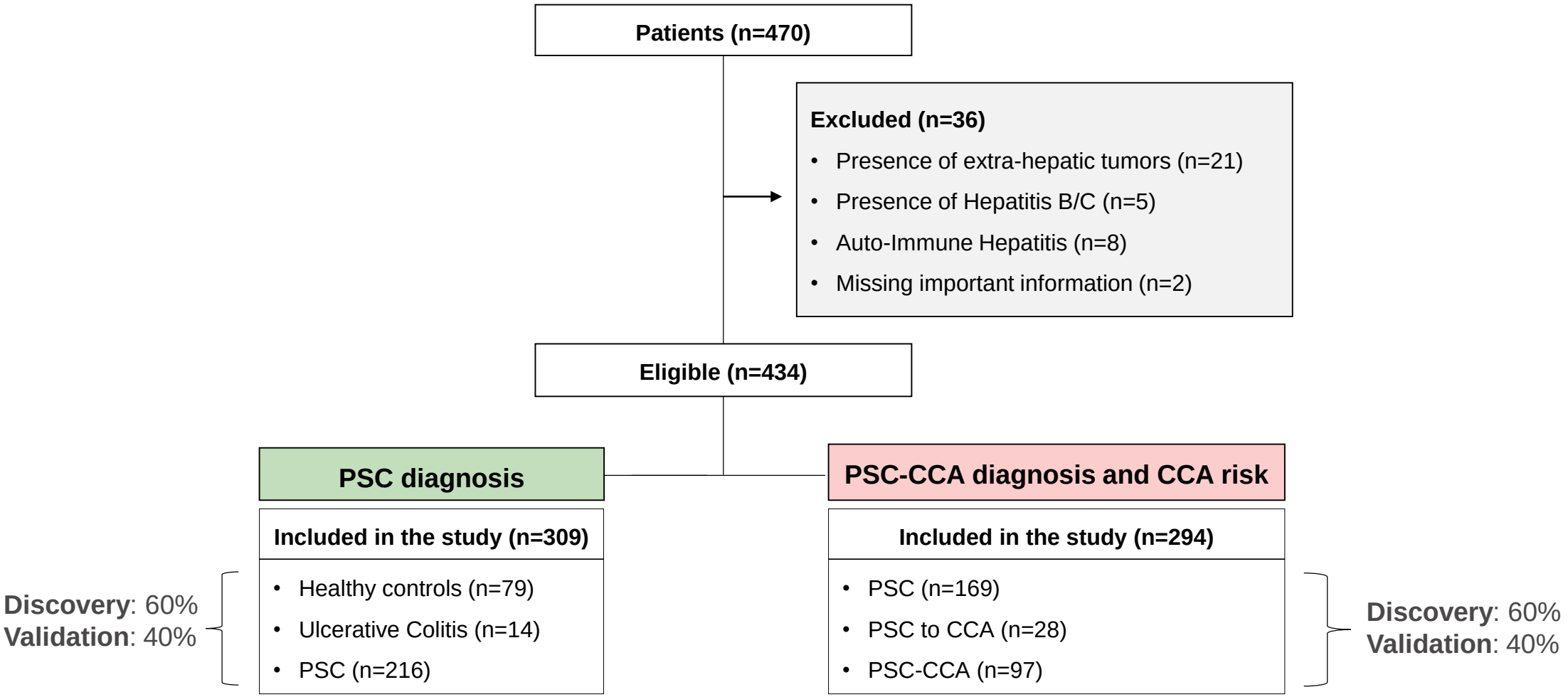
Lewis Roberts (USA)

IPSCSG International PSC Study Group
European Network for the Study of Cholangiocarcinoma
PSC PARTNERS SEEKING A CURE pscpartners.org
PSC Support
European Cholangiocarcinoma Network COST ACTION CA18122
Precision BTC Network

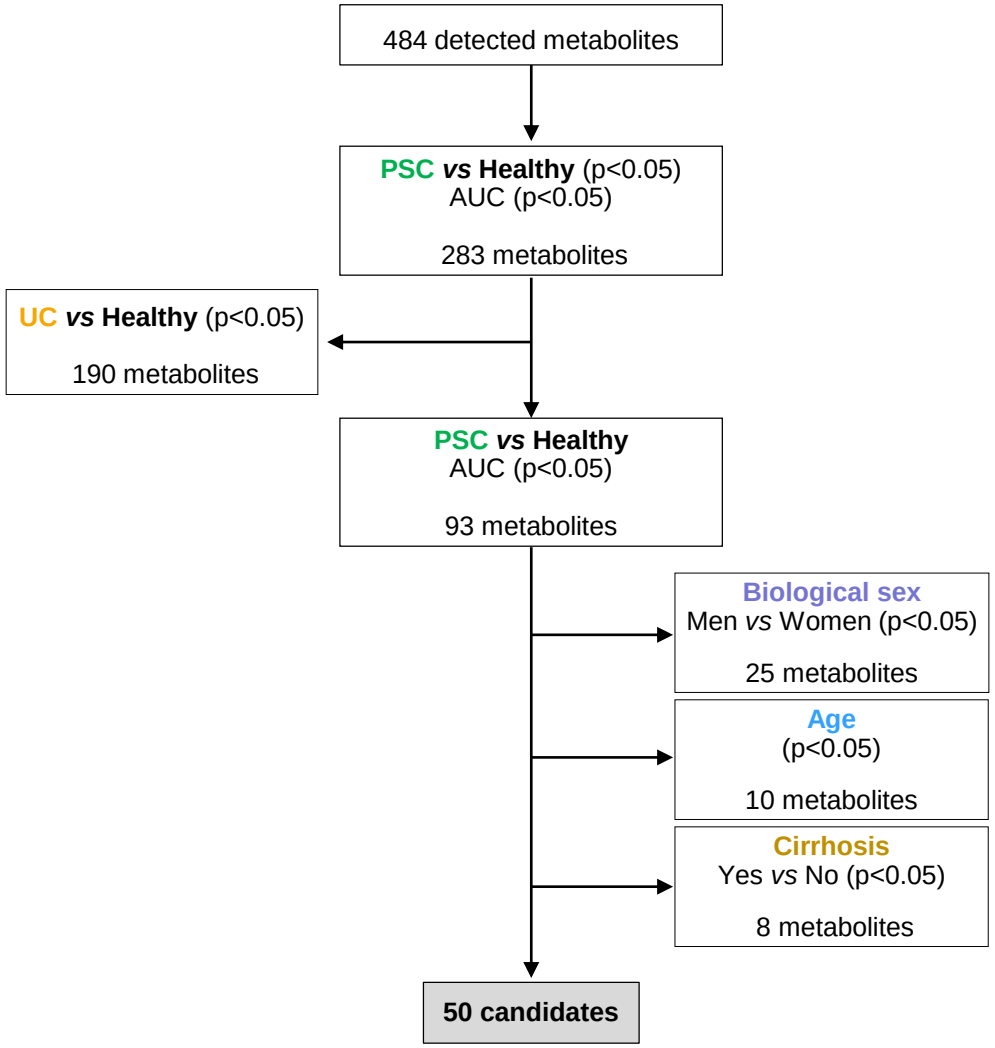
Multicentre international study

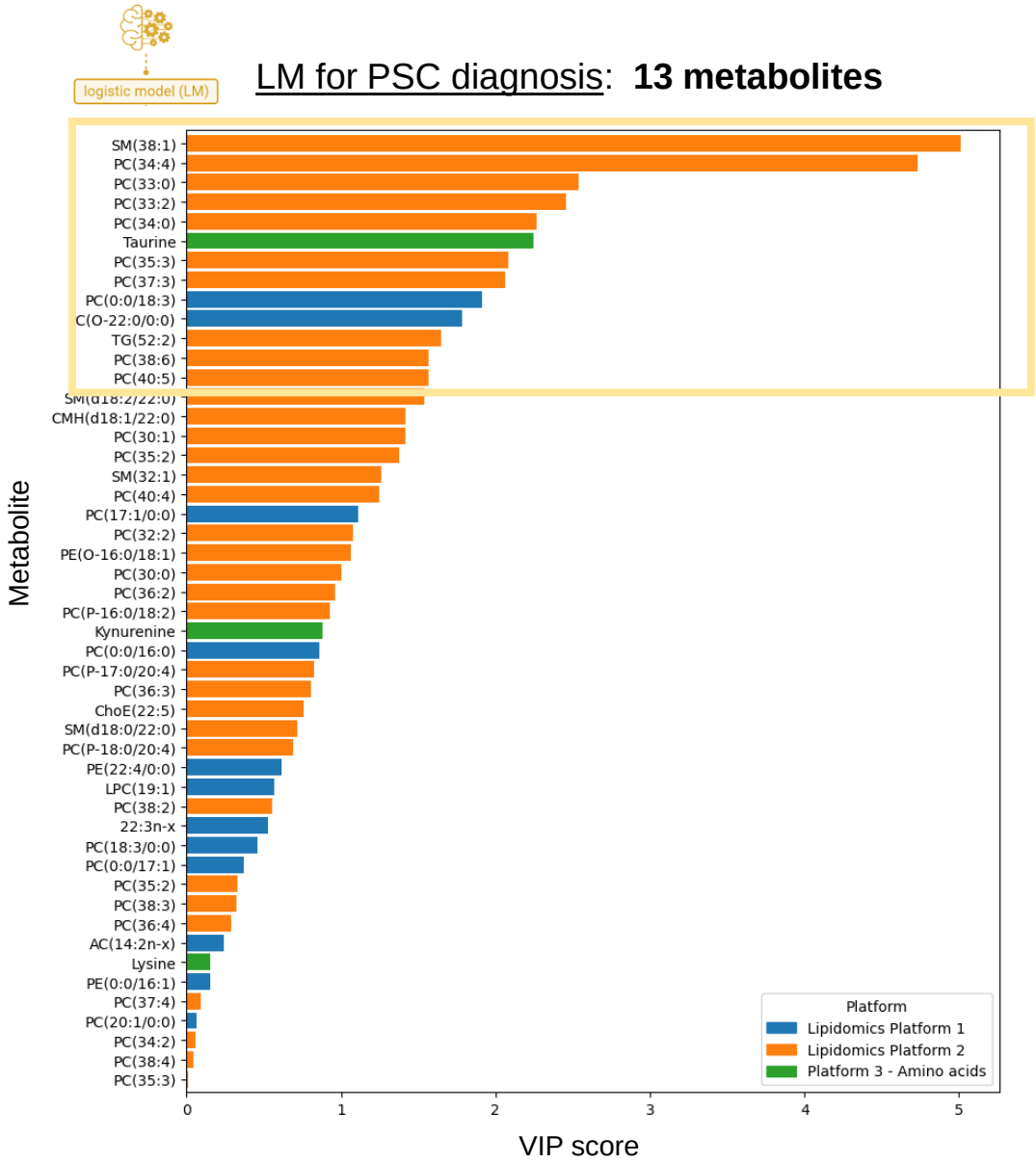


Objectives

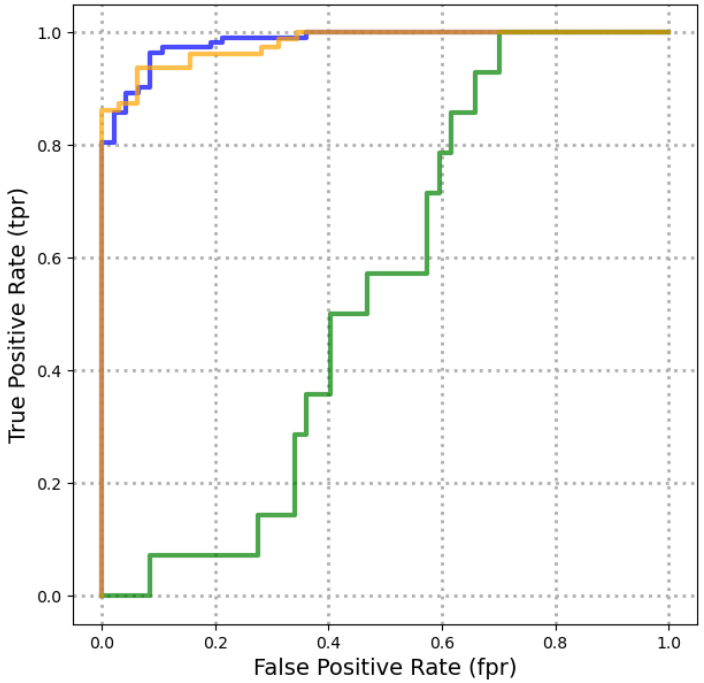
- **Diagnosis** of patients with PSC
- **Early diagnosis** of CCA in patients with PSC

Biomarkers for PSC diagnosis





Logistic model for PSC diagnosis



PSC *vs* Healthy

DISCOVERY: PSC (n=112) *vs* Healthy (n=47)

AUC **0.980**

VALIDATION: PSC (n=104) *vs* Healthy (n=32)

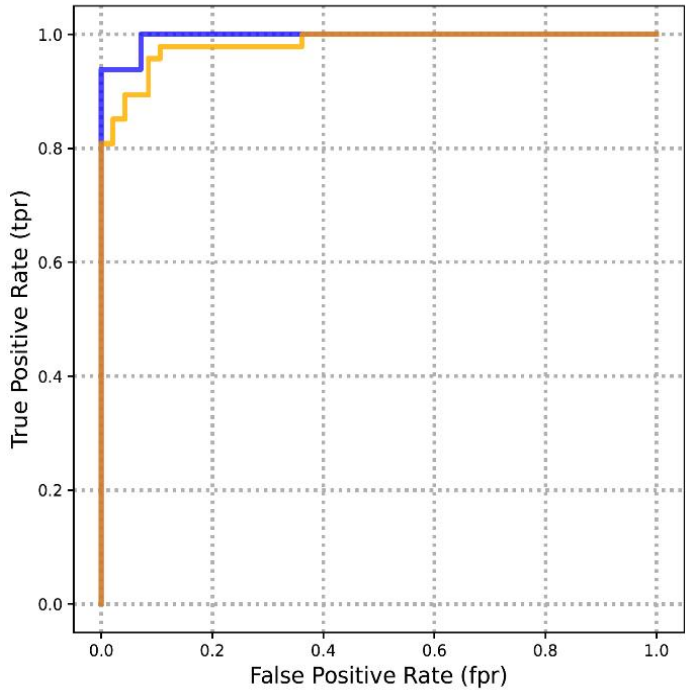
AUC **0.980**

UC *vs* Healthy

UC (n=14) *vs* Healthy (n=47)

AUC **0.540**

Logistic model for PSC diagnosis



PSC-UC *vs* UC

PSC-UC (n=65) *vs* UC (n=14)

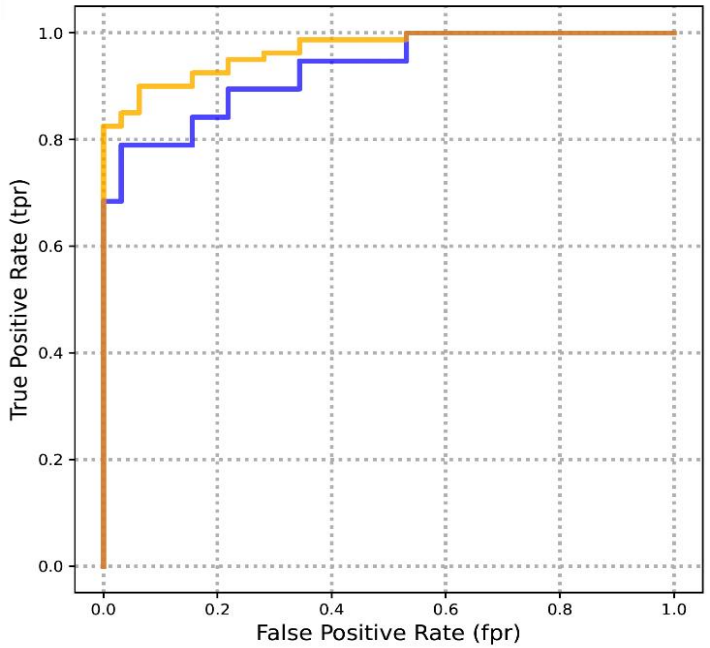
AUC **0.990**

PSC w/o IBD *vs* Healthy

PSC w/o IBD (n=47) *vs* Healthy (n=47)

AUC **0.980**

Logistic model for PSC diagnosis



PSC-Chron *vs* Healthy

PSC-Chron (n=19) *vs* Healthy (n=32)

AUC **0.930**

PSC Unspecified IBD *vs* Healthy

PSC Unspecified IBD (n=6) *vs* Healthy (n=32)

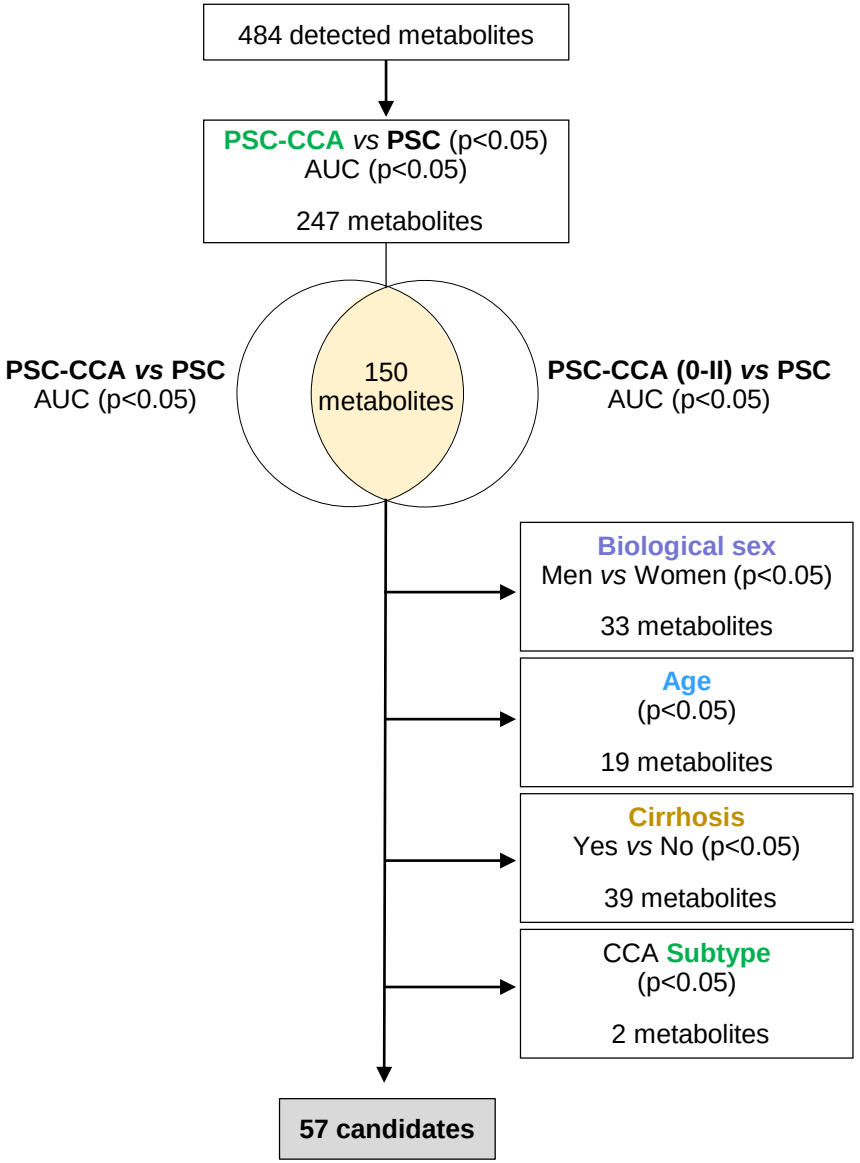
AUC **0.980**

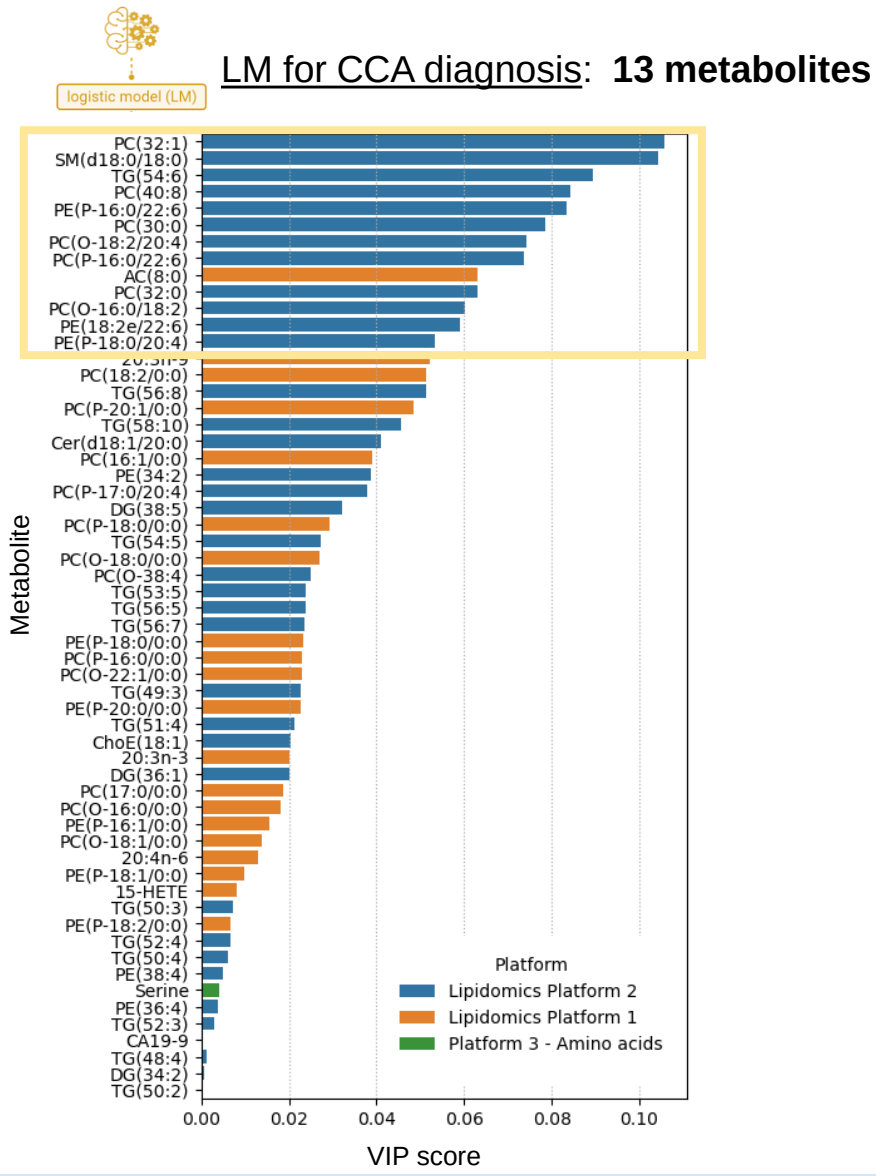
Objectives

Diagnosis of patients with PSC

Early diagnosis of CCA in patients with PSC

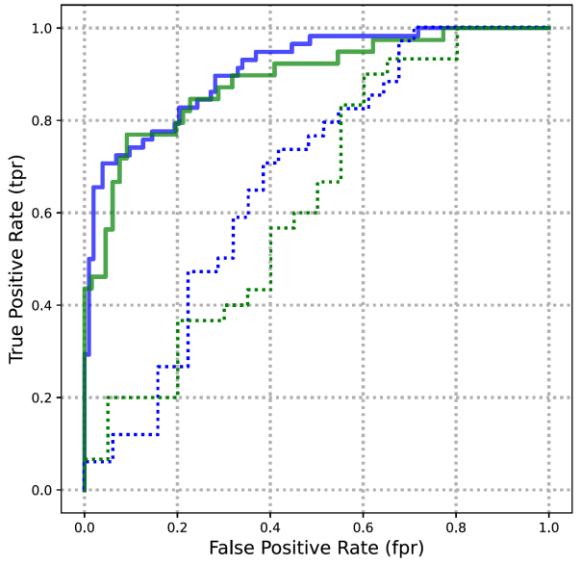
Biomarkers for early CCA diagnosis in patients with PSC





Logistic model for CCA diagnosis in PSC

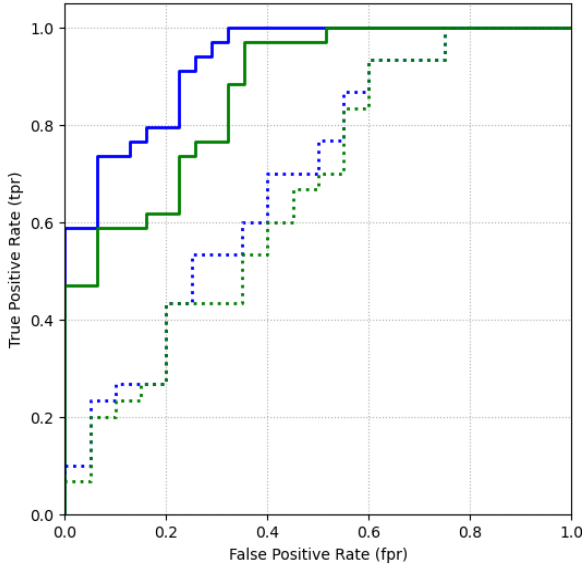
PSC-CCA *vs* PSC



DISCOVERY TEST **AUC 0.910**
--- CA19-9 AUC 0.670

VALIDATION TEST **AUC 0.890**
--- CA19-9 AUC 0.630

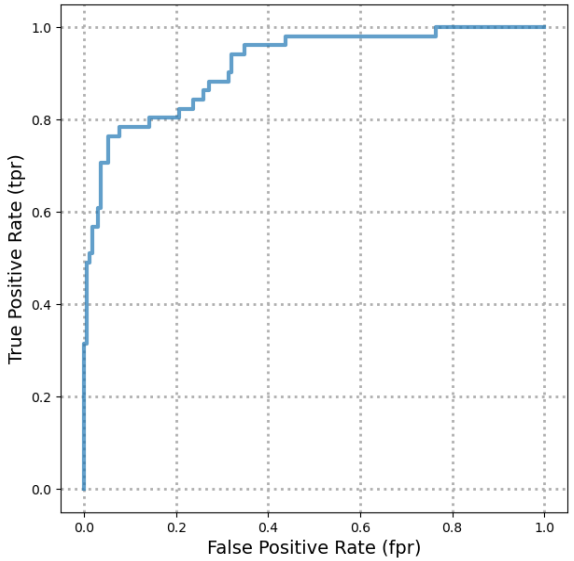
Early PSC-CCA (0-II) *vs* PSC



DISCOVERY TEST **AUC 0.930**
--- CA19-9 AUC 0.690

VALIDATION TEST **AUC 0.870**
--- CA19-9 AUC 0.660

Low CA19-9 PSC-CCA *vs* PSC

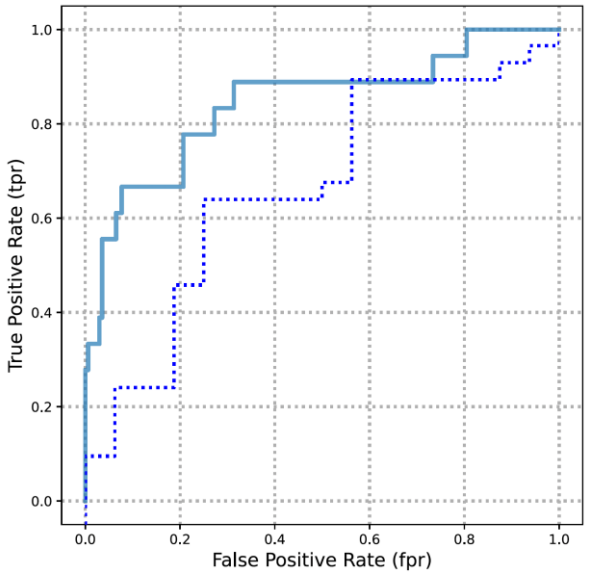


LOW CA19-9 (<37 IU/mL)

PSC-CCA **AUC 0.920**

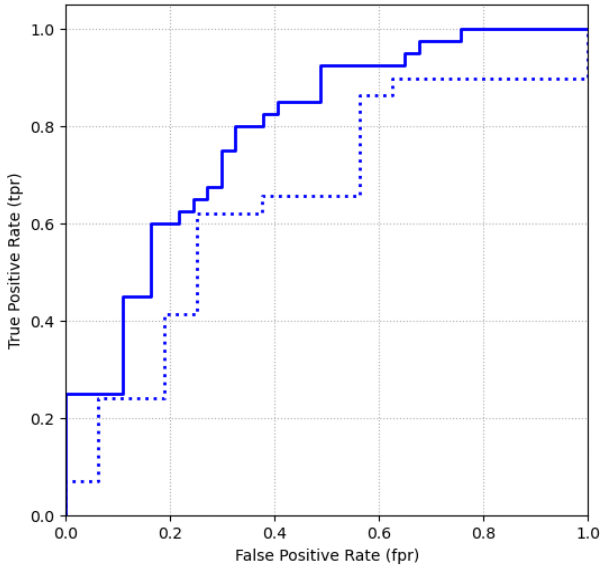
Diagnostic logistic model for risk stratification in PSC

PSC to CCA (<1 year) *vs* PSC



TEST	**AUC 0.840**
--- CA19-9	AUC 0.680

PSC to CCA (>1 year) *vs* PSC



TEST	**AUC 0.790**
--- CA19-9	AUC 0.650

Conclusions

- **Serum metabolomic profiling** represents a useful strategy for biomarker discovery in PSC
- **New tests combining specific metabolites** allow the diagnosis of PSC, CCA and the risk stratification
- **Next steps** are ongoing for **clinical implementation**


PSC
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International PSC Study Group


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Albireo


IPSEN
Innovation for patient care


rubió
Metabolomics


Jazz Pharmaceuticals

Acknowledgements

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Gonzalo Crespo/Tino Fondevilla (Spain)

Lewis Roberts (USA)

MISSION: Find a cure and improve the quality of life for patients with cholangiocarcinoma

VISION: A world free of cholangiocarcinoma

Cholangiocarcinoma Foundation®

Our Core Values

Founded in 2006, CCF has grown to become the leading global resource in research, education, and public awareness.

PATIENTS FIRST

We always put patients first. Our goal is to improve their treatment options and find a cure.

INNOVATION

We provide vital resources, education, and support to cholangiocarcinoma patients and their families.

COLLABORATION

We lead collaborative efforts, bringing scientists, clinicians, and healthcare providers together to share research, resources, and funding.

URGENCY

We urgently improve methodologies, technologies, and partnerships to energize and drive our programs, research, and funding strategies.

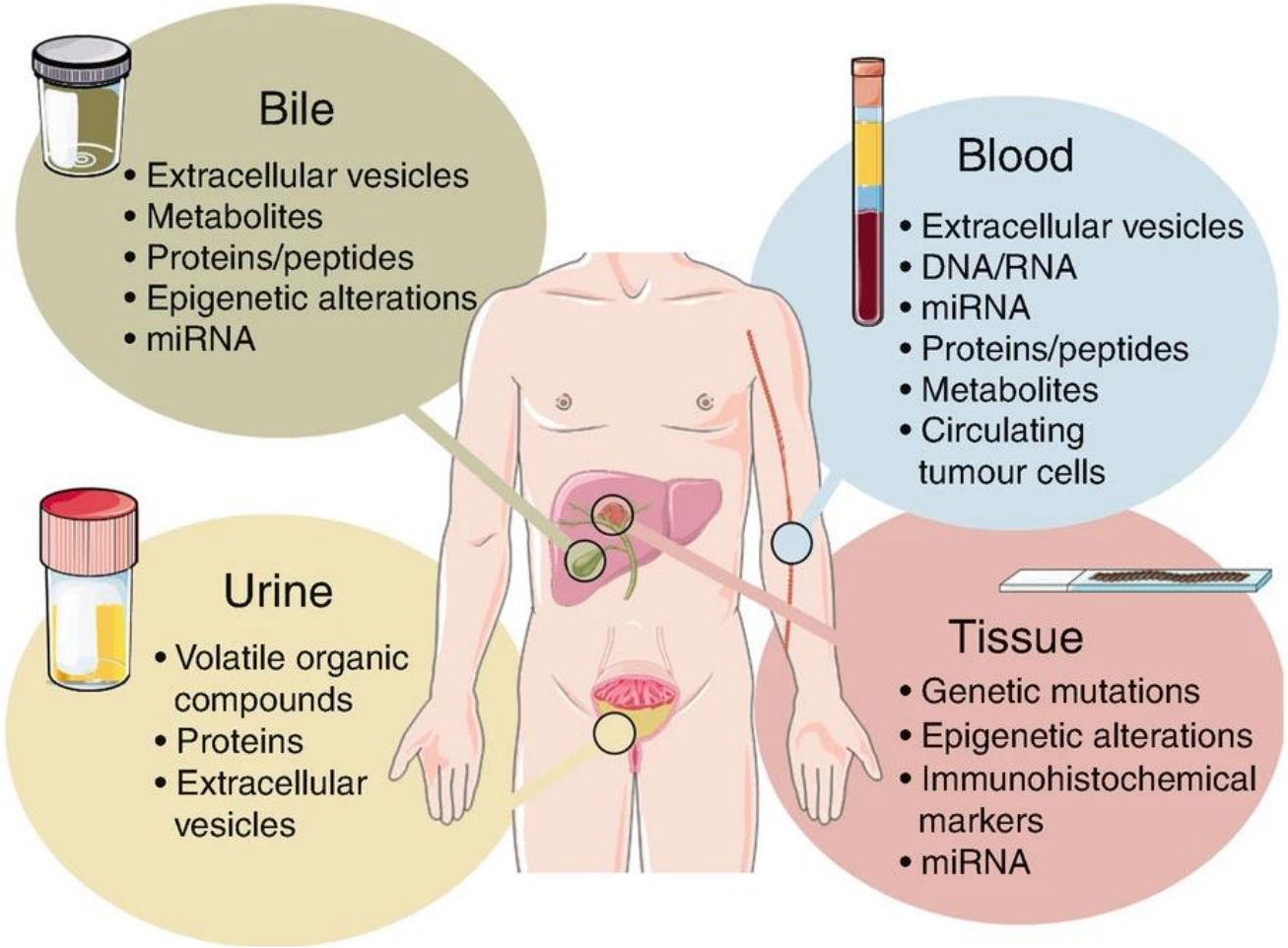
How we use biomarkers in patients with cholangiocarcinoma

A biomarker is a **measurable indicator** of a **biological process, condition, or disease**. It can be found in blood, other body fluids, tissues, or measured through imaging or physical signs.

In plain English:
A biomarker is anything we can measure in the body that tells us what's going on - whether someone is:

- *healthy*
- *sick*
- *if they may be suitable for treatment*
- *or how they're responding to treatment*

How we use biomarkers in patients with cholangiocarcinoma



García-Sampedro et al (2021). Established and Emerging Biomarkers for Prediction, Early Detection, and Prognostication of Cholangiocarcinoma. In: Tabibian, J.H. (eds) Diagnosis and Management of Cholangiocarcinoma. Springer, Cham.

Biomarkers may have different purposes in cancer

PROGNOSTIC

- Is a patient likely to develop cancer
- If already has cancer, who will do well

Adapted from https://www.meditrial.net/2022/09/clinical-trials-how-biomarkers-help-research/

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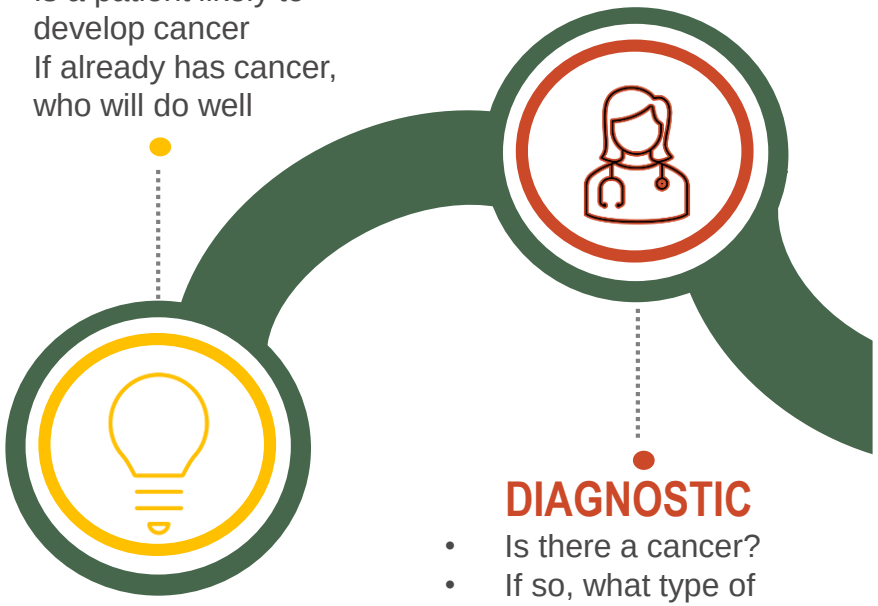

DIAGNOSTIC

- Is there a cancer?
- If so, what type of cancer is it?

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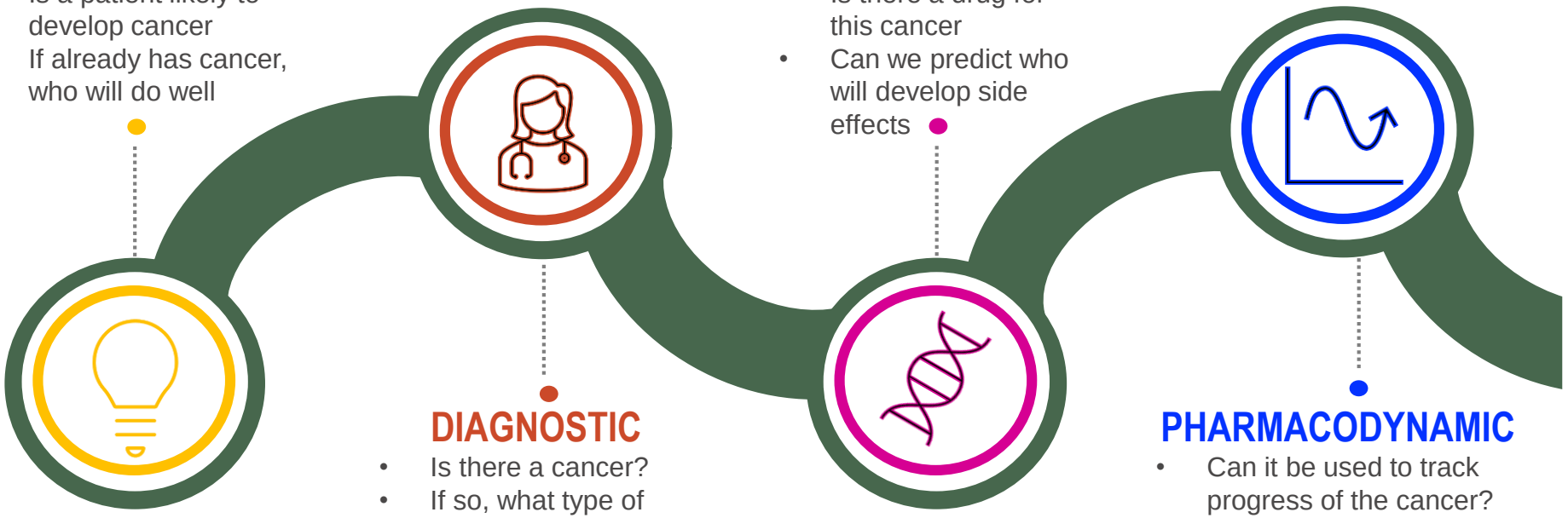

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PREDICTIVE

- Is there a drug for this cancer
- Can we predict who will develop side effects

PHARMACODYNAMIC

- Can it be used to track progress of the cancer?

Adapted from https://www.meditrial.net/2022/09/clinical-trials-how-biomarkers-help-research/

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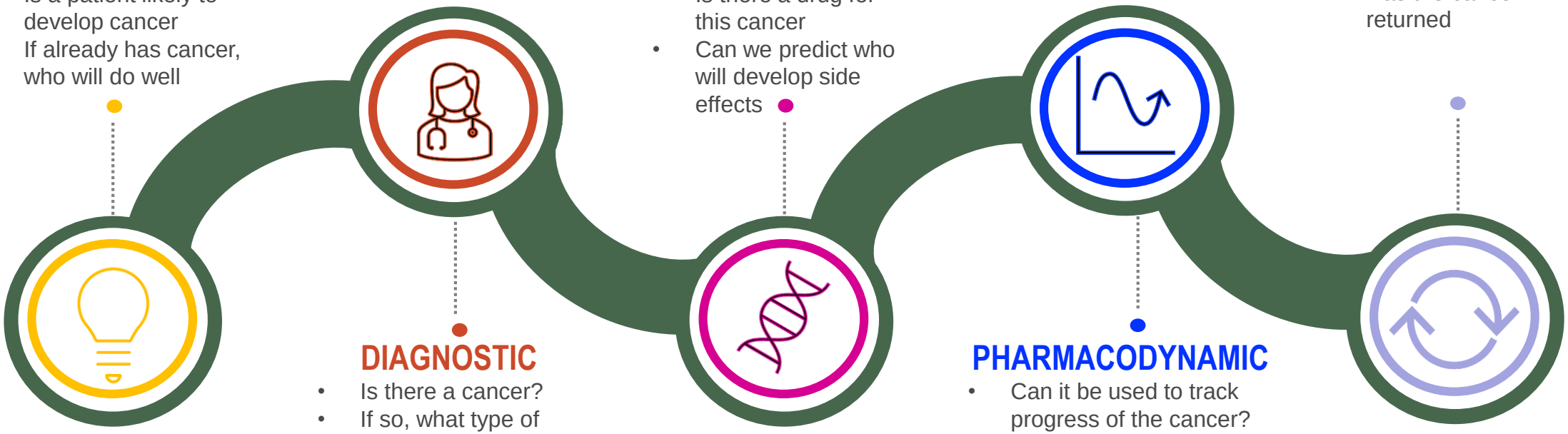

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- Has the cancer returned

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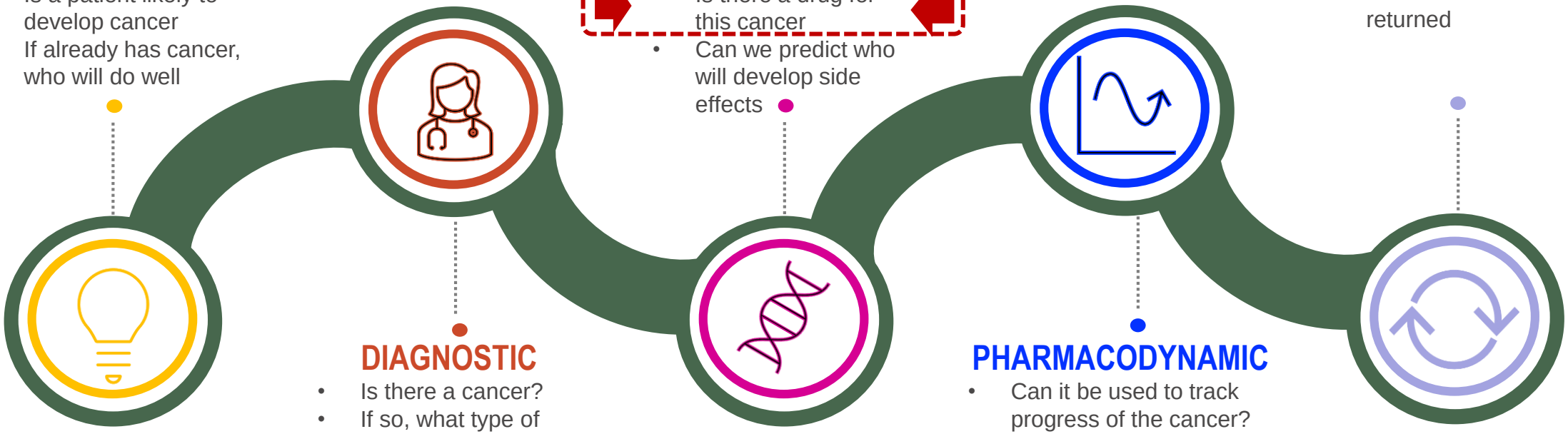

	PROGNOSTIC	DIAGNOSTIC	PREDICTIVE	PHARMACODYNAMIC	RECURRENCE
CA19-9	✓	✗	✗	✓	✓
DPYD	✗	✗	✓	✗	✗

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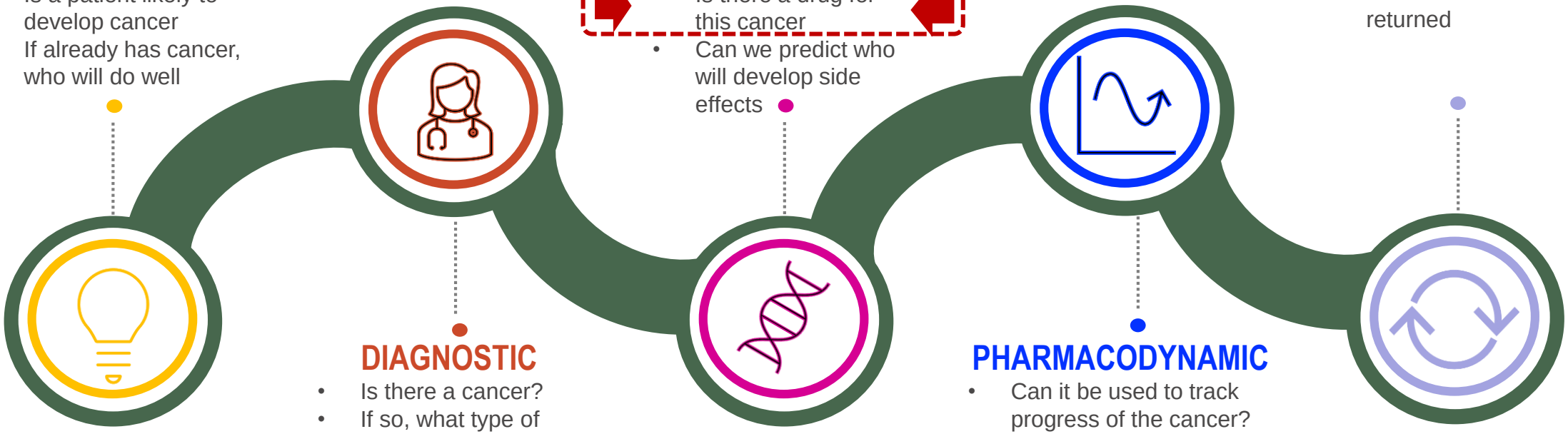
- Can it be used to track progress of the cancer?

RECURRENCE

- Has the cancer returned

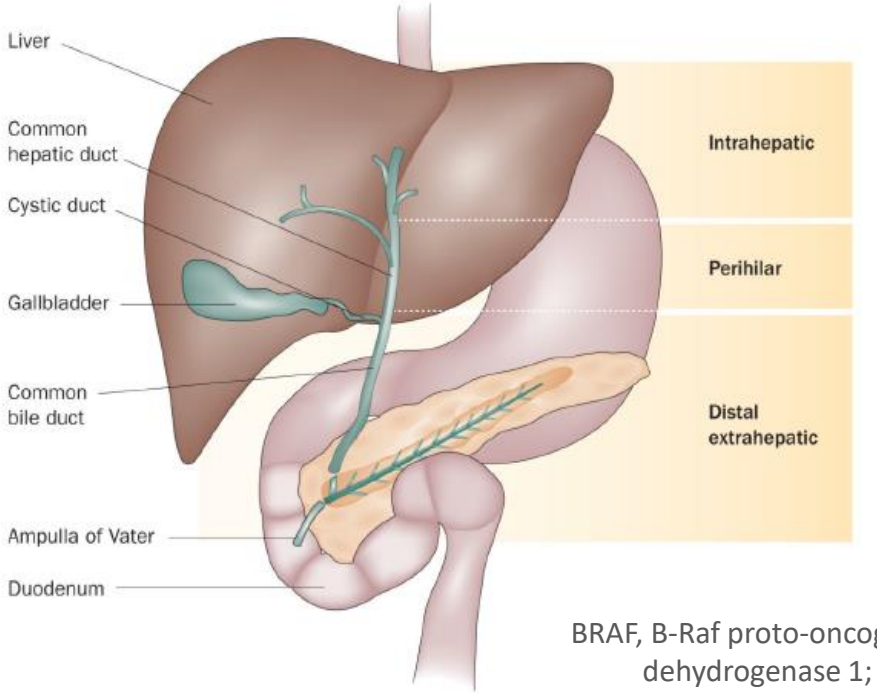


	PROGNOSTIC	DIAGNOSTIC	PREDICTIVE	PHARMACODYNAMIC	RECURRENCE
CA19-9	✓	✗	✗	✓	✓
DPYD	✗	✗	✓	✗	✗

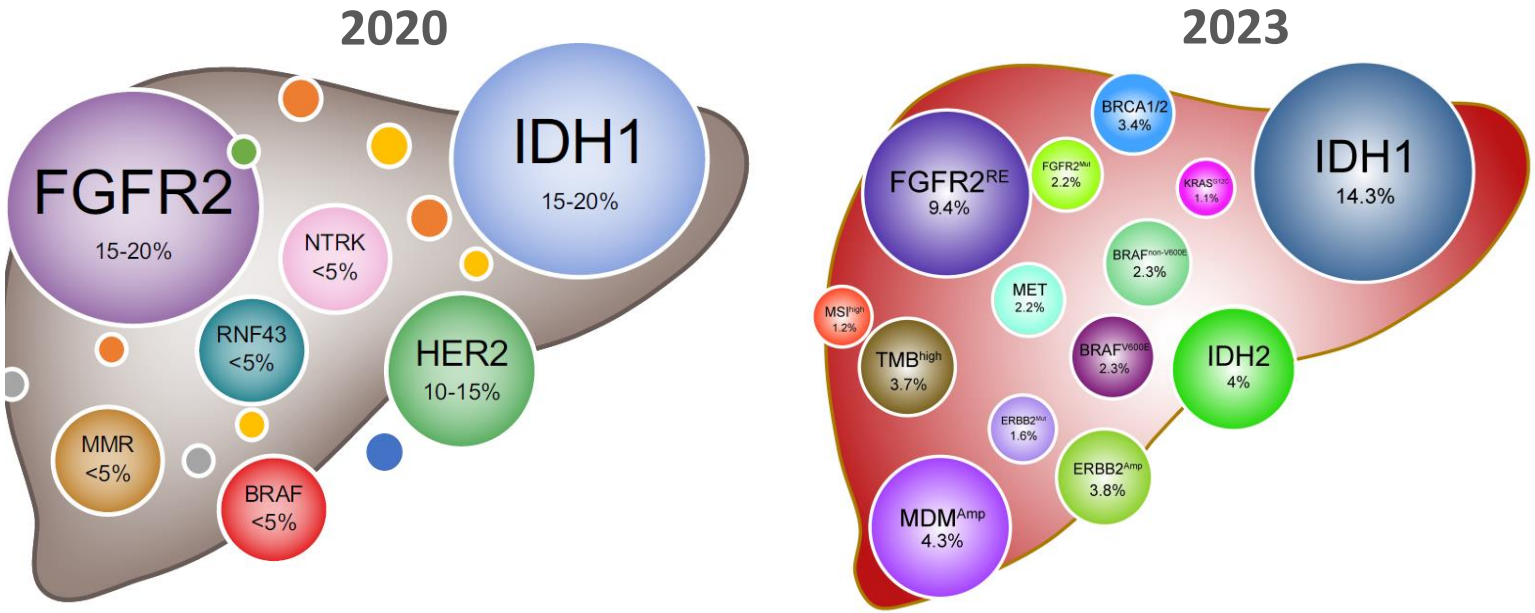
Adapted from https://www.meditrial.net/2022/09/clinical-trials-how-biomarkers-help-research/

From anatomical to molecular subgroups

Anatomical[1]



Molecular [2,3]

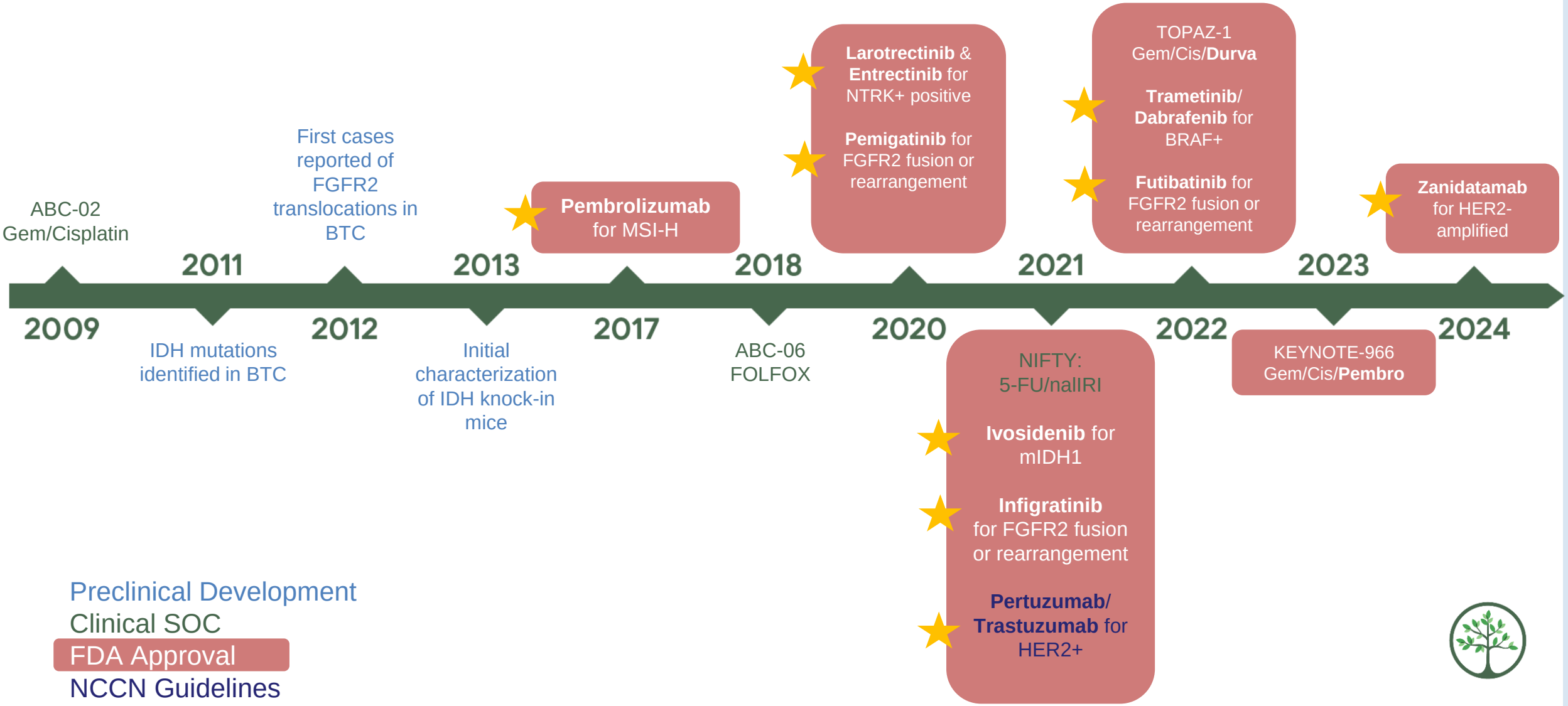


BRAF, B-Raf proto-oncogene; FGFR2, fibroblast growth factor receptor 2; HER2, human epidermal growth factor receptor 2; IDH1, isocitrate dehydrogenase 1; MMR, mismatch repair deficiency; NTRK, neurotrophic receptor tyrosine kinase; RNF43, ring finger protein 43.

Progress is being made every year: new targets, new therapies, new combinations

1. Blechacz et al *Nat Rev Gastroenterol Hepatol* 2011;8:512–22
2. Lamarca et al *J Hepatol* 2020 Jul;73(1):170-185
3. Kendre et al. *J Hepatol* 2023 Mar;78(3):614-626

Drug Development Timeline



Preclinical Development
Clinical SOC
FDA Approval
NCCN Guidelines

Biomarkers Matter

For cancer patients, biomarker testing may provide access to effective, personalized treatment options and clinical trials. Learn more about biomarkers as it related to you:

BIOMARKER INFO FOR:

Cholangiocarcinoma Patients & Caregivers

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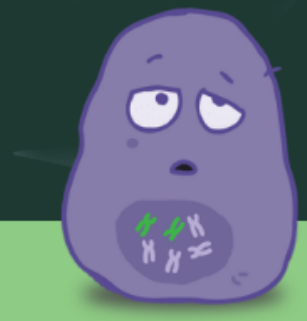
BIOMARKER INFO FOR:

Other Types of Cancer Patients

LEARN MORE →



BIOMARKER INFO FOR:

Healthcare Professionals

LEARN MORE →

The Cholangiocarcinoma Foundation has created this important educational campaign for the benefit of its constituency and the broader community. To that end, the Foundation encourages broad dissemination of these resources and materials. Promotion of the Biomarkers Matter campaign by third parties does not indicate endorsement by the Foundation of those third parties or any of their programs, activities or products.

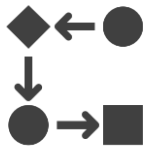
Take home messages

- **Biomarkers are not all the same** and are being developed for specific purposes

- **New tests combining specific metabolites** allow the **diagnosis** of PSC, CCA and the risk stratification

- **Major advances** in identifying **predictive biomarkers linked to new therapies**

MSI-H	**dMMR**	**FGFR2**	**IDH1**
HER2	**BRAF^{V600E}**	**NTRK**	



BAP-1	Claudin 18.2	KRAS	TROP2
B7H4	MDM2	MTAP	

Cholangiocarcinoma Foundation®

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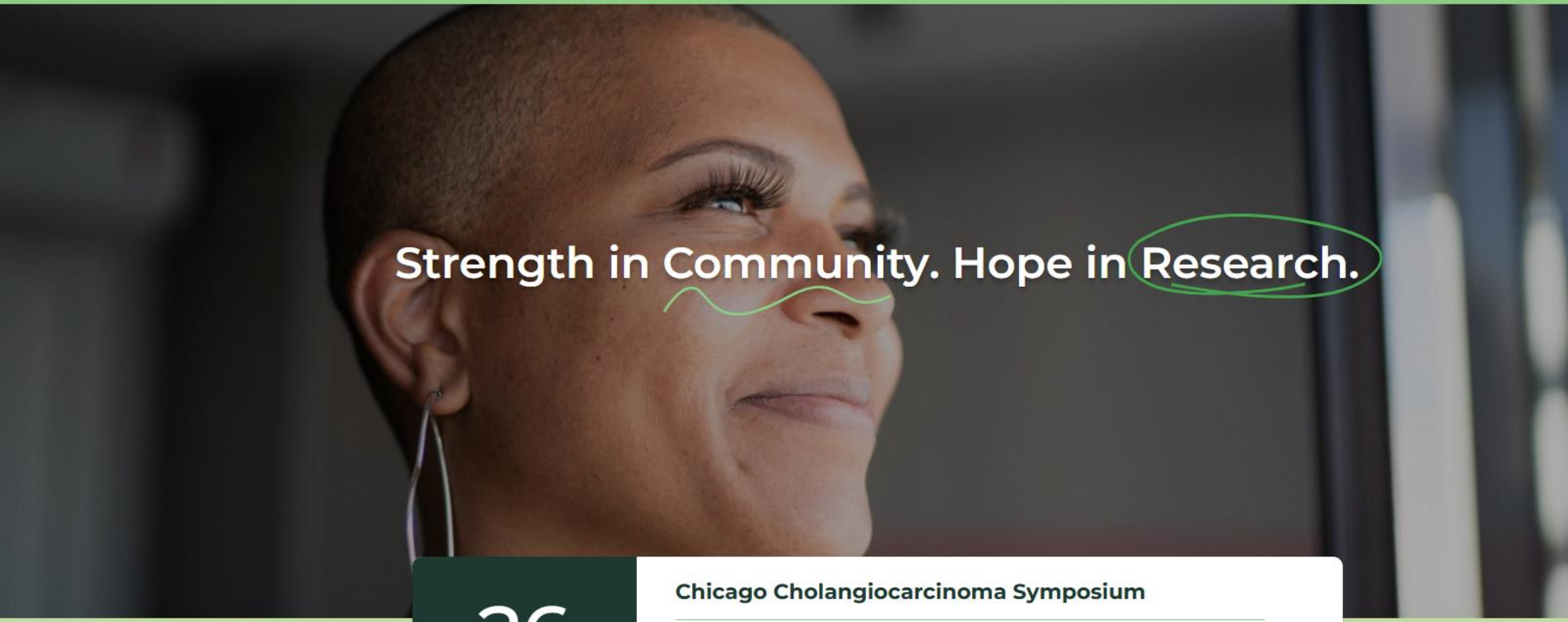

26
SEPT.

Chicago Cholangiocarcinoma Symposium

Hosted with the University of Chicago Medicine, this event provides an opportunity for patients, caregivers, and healthcare providers to learn more about treatments and support, get their questions answered, and connect with others facing similar paths. **Please register today**.