# Cholangiocarcinoma: Disease State Overview


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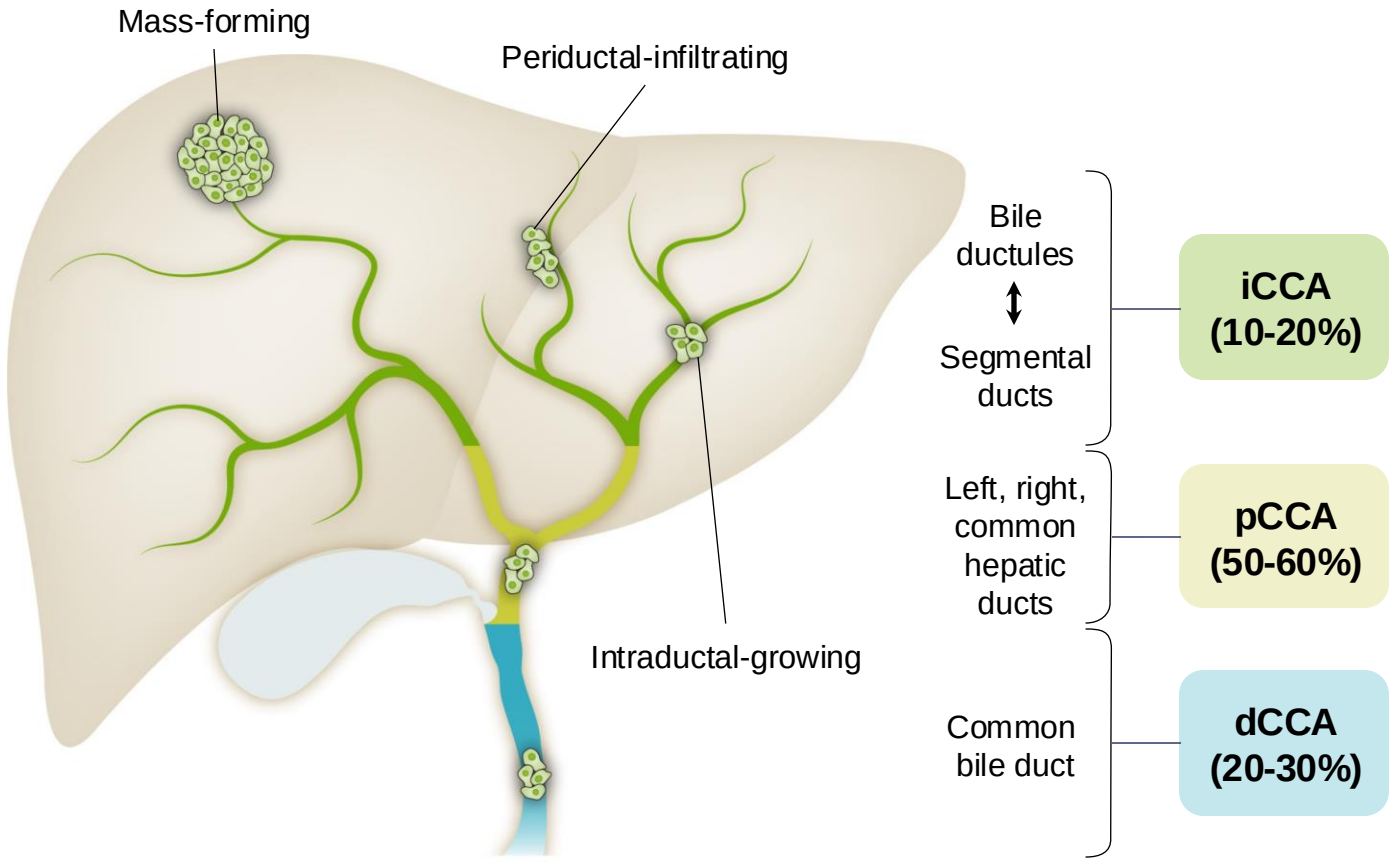
# Epidemiology and Etiology

# CCAs Are Heterogeneous Tumors Arising in the Bile Duct

- CCAs are heterogeneous epithelial tumors originating from cholangiocytes in the biliary tree[1-3]
- CCAs are classified into different anatomical subtypes based on location in the biliary tract:[1-4]
  - Intrahepatic
  - Extrahepatic, which is further divided into:
    - Perihilar
    - Distal
- Each anatomical subtype has different clinical and pathological characteristics, including different patterns of genomic alterations[1,2]

## Anatomic classification of CCA[1]




dCCA, distal CCA; iCCA, intrahepatic CCA; pCCA, perihilar CCA.

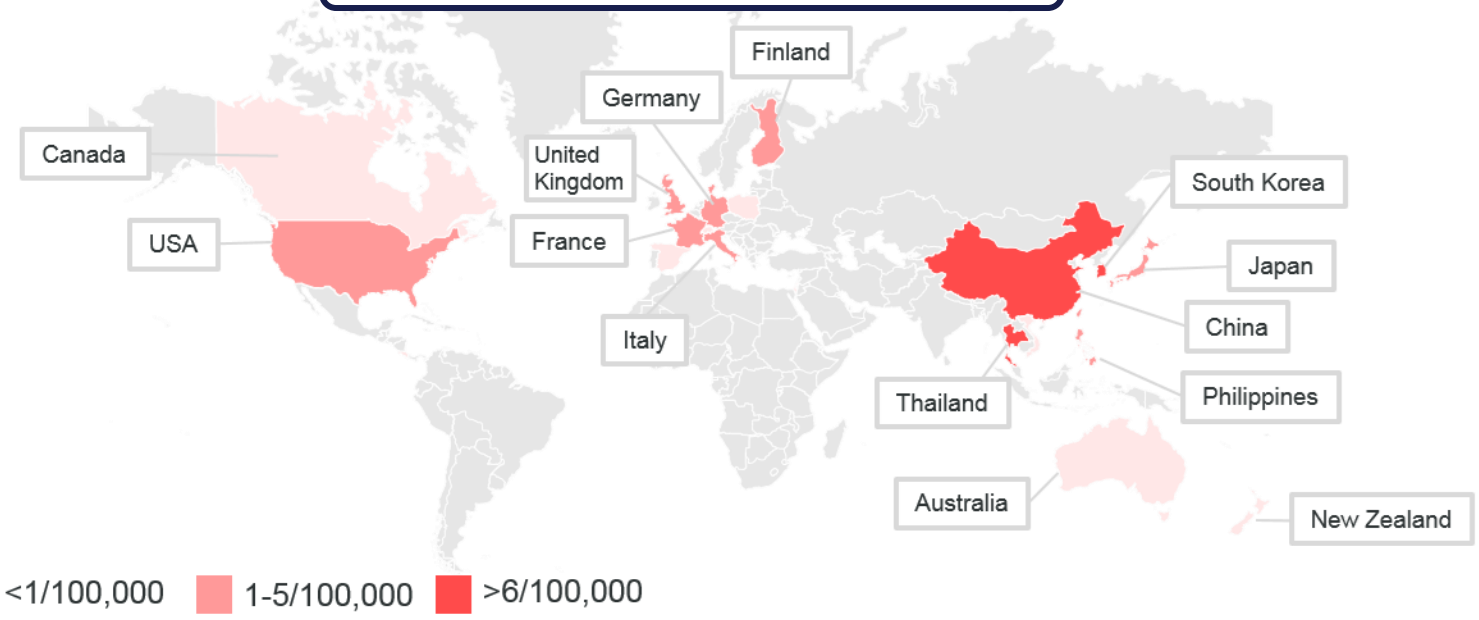
1. Banales JM, et al. *Nat Rev Gastroenterol Hepatol*. 2020;17:557-588. Figure reproduced under the terms of the Creative Commons Attribution 4.0 International (CC BY 4.0) license (https://creativecommons.org/licenses/by/4.0/), only edits for style were made. 2. Blechacz B. *Gut Liver*. 2017;11:13-26. 3. Malenica I, et al. *Cancers (Basel)*. 2020;12:2190. 4. Huguet JM, et al. *World J Clin Cases*. 2019;7:1732-1752.

# The Incidence of CCA Varies Significantly in Different Regions of the World

Account for **3%** of all GI tumors[1]

**~15%** of all primary hepatic tumors[1]

## Incidence of CCA worldwide[1,2]




- The worldwide epidemiology of CCA is widely variable, with generally lower incidences in Western vs Asian countries[3]
- Parasitic infections are key risk factors in higher risk Southeast Asian countries, with South Korea, China, and Thailand having the highest incidence of CCA[1,4]
- Between 2000 and 2015 in the US, 63% of patients diagnosed with CCA were >65 years of age[5]

GI, gastrointestinal; US, United States.

1. Banales JM, et al. *Nat Rev Gastroenterol Hepatol*. 2020;17:557-588. 2. Banales JM, et al. *Nat Rev Gastroenterol Hepatol*. 2016;13:261-280. Figure reproduced under the terms of the Creative Commons Attribution 4.0 International (CC BY 4.0) license (https://creativecommons.org/licenses/by/4.0/), only edits for style were made. 3. Baria K, et al. *Gastro Hep Advances.* 2022;1:618-626. 4. Florio AA, et al. *Cancer.* 2020;126:2666-2678. 5. Gad MM, et al. *Clin Res Hepatol Gastroenterol*. 2020;44:885-893.

# The Increasing Incidence of iCCA

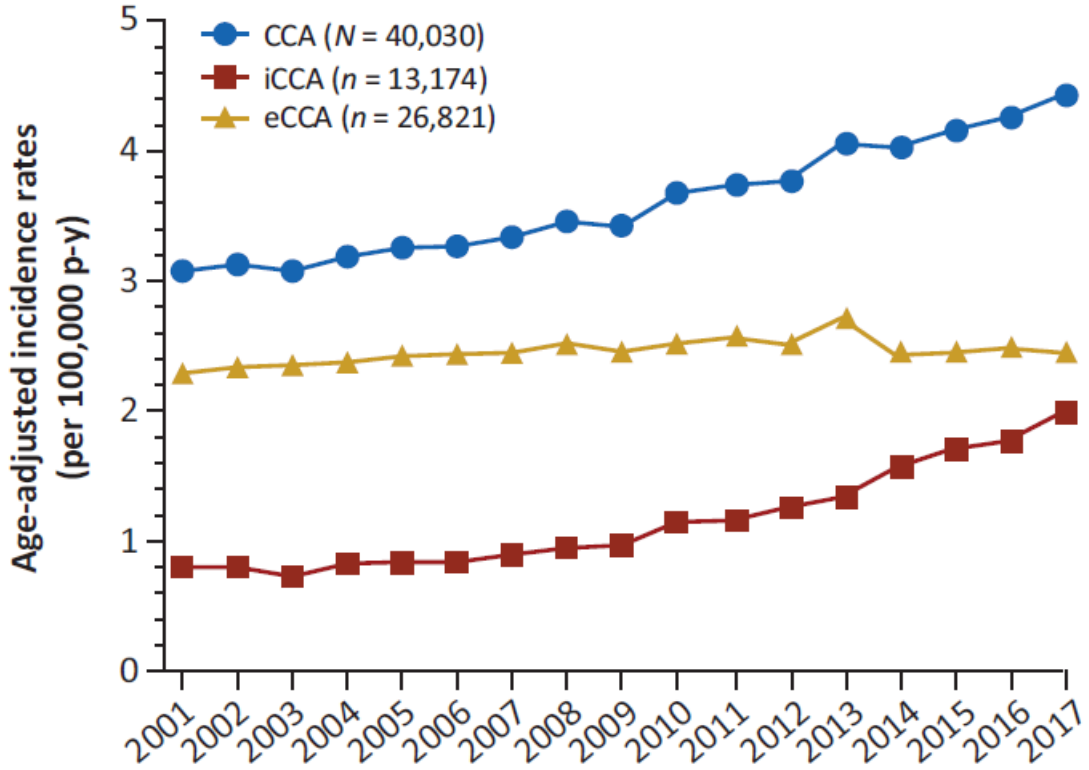
| Year | Age-Adjusted Incidence of CCA |
|---|---|
| 2001 | 3.08 per 100,000 |
| 2017 | 4.43 per 100,000 |

According to an analysis of the SEER database, the age-adjusted incidence rates of CCA have increased by almost 44% over the past ~20 years

| Year | Age-Adjusted Incidence of iCCA | Age-Adjusted Incidence of eCCA |
|---|---|---|
| 2001 | 0.80 per 100,000 | 2.28 per 100,000 |
| 2017 | 1.99 per 100,000 | 2.45 per 100,000 |

The overall growth in the incidence rate of CCA is largely attributable to iCCA, which has increased by 149% over the past ~20 years

## Age-Adjusted Incidence of CCA, iCCA and eCCA in the USA (2001-2017, per 100,000 p-y)




p-y, person-years; SEER, Surveillance, Epidemiology, and End Results.

# Most Cases of CCA Occur in the Absence of Evident Risk Factors

- The majority of CCAs (70%) occur sporadically without any apparent cause[1]
- However, there are risk factors strongly associated with CCA, the most relevant of which are PSC, liver flukes, and virus-related liver diseases[2]

## Risk Factors Associated With CCA[1-3]

### Parasitic infections

Liver flukes (from ingesting raw, undercooked, or pickled food; mostly in Southeast Asia)

- *Opisthorchis viverrini*
- *Clonorchis sinensis*

### Coexisting liver/ duct diseases

- HBV-related diseases (mostly in Asia)
- HCV-related diseases (mostly in Western countries)
- Liver cirrhosis
- Gallstones
- Bile duct cysts
- Choledochal cysts

### Bile duct autoimmune diseases

- PSC (with or without IBD; mostly in Western countries)

### General

- Age >65 years
- Obesity
- Tobacco and alcohol use
- Aspirin use
- Printing factory chemicals
- Type 2 diabetes mellitus
- Hypertension

HBV, hepatitis B virus; HCV, hepatitis C virus; IBD, inflammatory bowel disease; PSC, primary sclerosing cholangitis.

1. Kirstein MM, Vogel A. *Visc Med*. 2016;32:395-400. 2. Bañales JM, et al. *Nat Rev Gastroenterol Hepatol*. 2016;13:261-280. 3. Clements O, et al. *J Hepatol.* 2020;72:95-103.

# CCA Is Asymptomatic Until Advanced Stages

- 20-25% of CCA diagnoses result from incidental findings (eg, abnormal liver function test results)[1,2]
- Symptoms of CCA are often nonspecific and are usually limited until the tumor grows and begins to block the bile duct[1-3]
- Symptoms also tend to depend on whether the cancer is intrahepatic or extrahepatic[3]
  - As eCCA is more likely to severely obstruct biliary drainage, it is more likely than iCCA to present with symptoms[3]
  - In patients with eCCA, 90% present with painless jaundice, and 10% present with acute cholangitis[3]

## Symptoms of Advanced CCA[1-3]

- Jaundice
- Cholangitis
- Fatigue
- Light-colored/greasy stools
- Abdominal pain
- Weight loss/anorexia
- Nausea
- Night sweats

eCCA, extrahepatic CCA.

1. Banales JM, et al. *Nat Rev Gastroenterol Hepatol*. 2016;13:261-280. 2. Forner A, et al. *Liver Int*. 2019;39(1 suppl):98-107. 3. Blechacz B, et al. *Nat Rev Gastroenterol Hepatol*. 2011;8:512-522.

# Bile Duct Obstruction Is a Common and Serious Complication of CCA

## Malignant biliary obstruction

- Complete surgical resection is the best potentially curative therapy[1]
- Many patients are not candidates for surgery and therefore require a palliative biliary stent[1,2]

## Biliary stenting

- Palliative biliary stenting helps relieve obstructive cholestasis and its associated conditions, such as pruritus, cholangitis, and pain[1]
- Endoscopic stenting can restore biliary drainage in almost 90% of patients, with the advantage of providing a more noninvasive and comfortable patient experience compared with percutaneous transhepatic cholangiography[1,2]



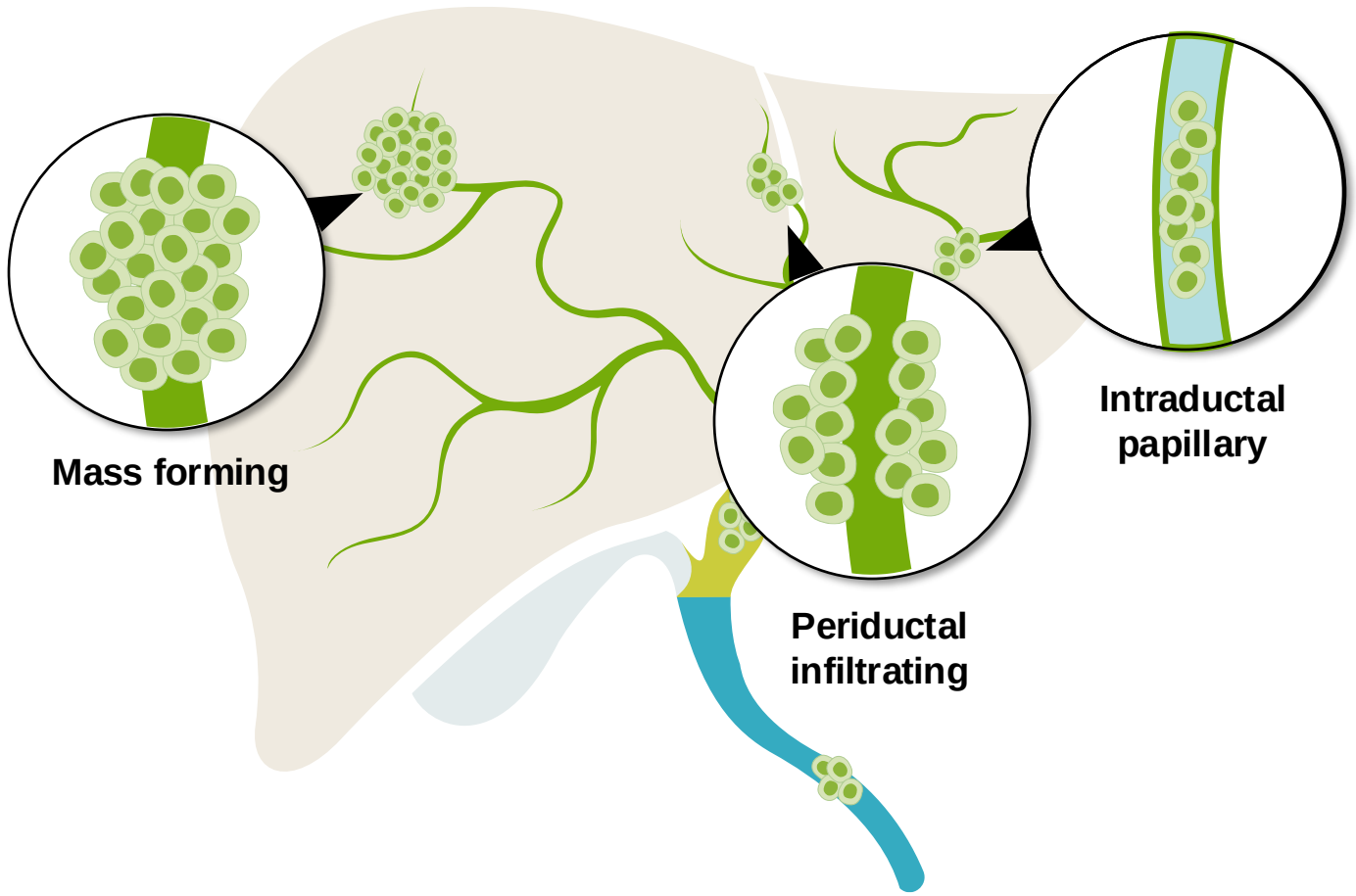
1. Kim JH. *Clin Endosc*. 2011;44:76-86. 2. Bertani H, et al. *World J Gastrointest Endosc*. 2015;7:582-592.

# Diagnosis, Staging, and Prognosis

# Growth Pattern and Cellular Classification of CCA

- CCAs are usually adenocarcinomas with varying degrees of differentiation; other histological subtypes are rare[1]
- CCA tumors present with 1 of 3 growth patterns according to anatomical location and morphology[1,2]
  - Mass forming
  - Periductal infiltrating
  - Intraductal papillary
- iCCAs predominantly present with a mass-forming (65%) growth pattern, followed by mixed-form (25%), periductal (6%), and intraductal (4%)[2]

## CCA Growth Patterns[1,2]



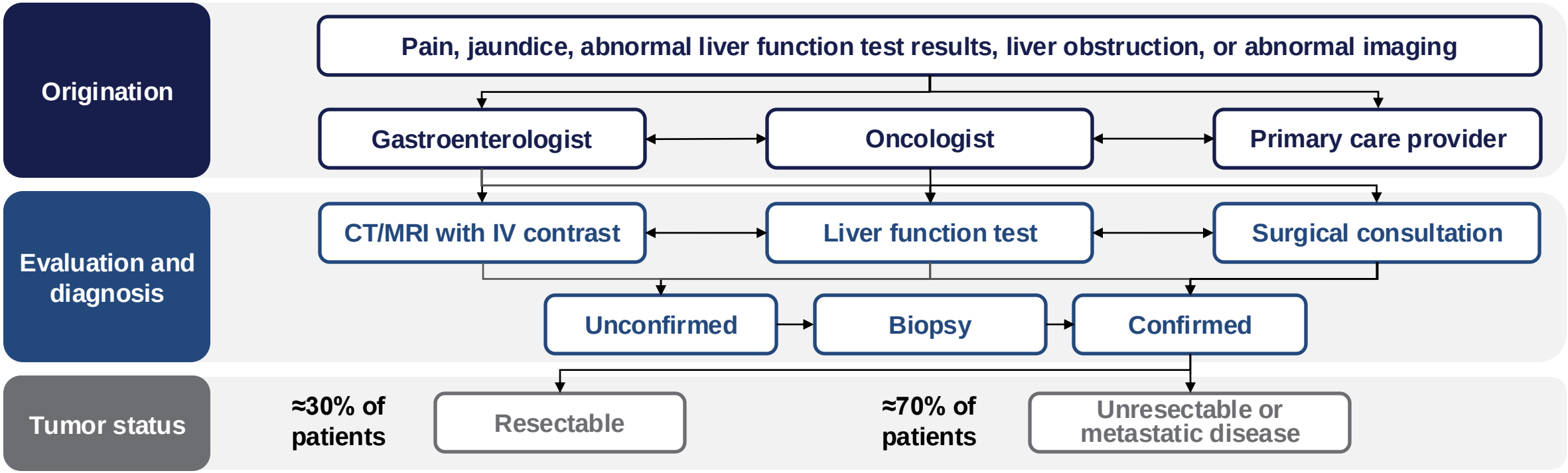



1. Bañales JM, et al. *Nat Rev Gastroenterol Hepatol*. 2016;13:261-280. 2. Vijgen S, et al. *Hepatobiliary Surg Nutr.* 2017;6:22-34.

# CCA Is A Diagnosis of Exclusion

- Diagnosis requires careful interpretation of clinical, radiological, and nonspecific histological and/or biochemical markers[1,2]
- CCA is usually diagnosed after metastasis when the disease is unresectable[2,3,5]

## Diagnosis of CCA[1,2,4,5]




CT, computed tomography; IV, intravenous; MRI, magnetic resonance imaging.

1. Bañales JM, et al. *Nat Rev Gastroenterol Hepatol*. 2016;13:261-280. 2. Blechacz B, et al. *Nat Rev Gastroenterol Hepatol.* 2011;8:512-522. 3. Valle JW, et al. *N Engl J Med*. 2010;362:1273-1281. 4. Razumilava N, Gores GJ. *Lancet*. 2014;383:2168-2179. 5. Valle JW, et al. *Cancer Discov.* 2017;7:943-962.

# Staging of CCA Is Defined by the 8th Edition of the *AJCC Cancer Staging Manual* TNM Model

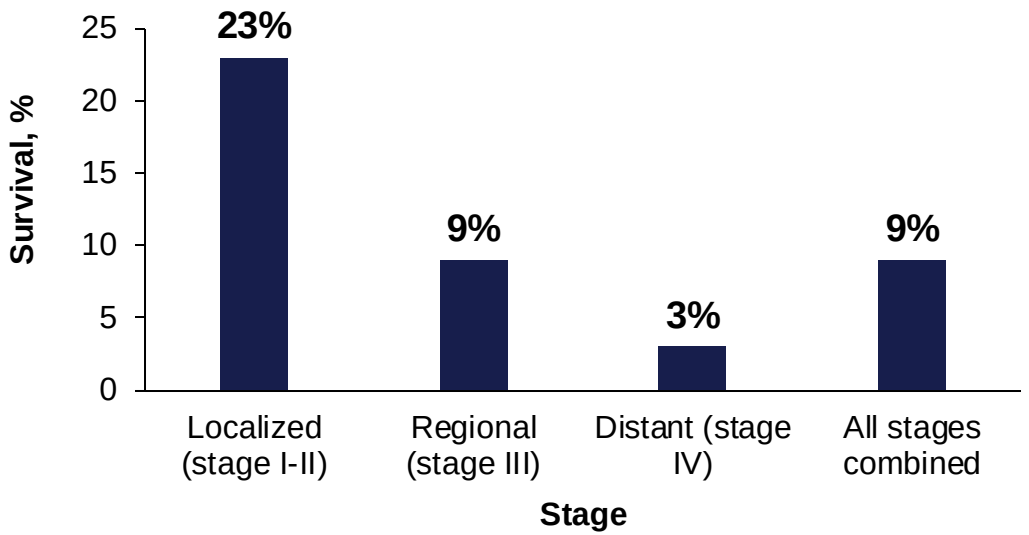
- iCCA, pCCA, and dCCA are staged using separate AJCC criteria[a]
- The different TNM criteria account for:
  - Location of the tumor (intrahepatic; proximity to the gallbladder, pancreas, duodenum, or other adjacent organs)
  - Potential areas of tumor invasion (eg, vasculature/arteries, peritoneum, muscles, adipose tissue)
  - Tumor size
  - Spread to specific local and regional lymph nodes

| iCCA | | pCCA | | dCCA | |
|---|---|---|---|---|---|
| **Stage** | **TNM** | **Stage** | **TNM** | **Stage** | **TNM** |
| 0 | Tis N0 M0 | 0 | Tis N0 M0 | 0 | Tis N0 M0 |
| IA-B | T1 N0 M0 | I | T1 N0 M0 | I | T1 N0 M0 |
| II | T2 N0 M0 | II | T2 N0 M0 | IIA | T1 N1 M0<br>T2 N0 M0 |
| | | | | IIB | T2 or 3 N1 M0<br>T3 N0 M0 |
| IIIA | T3 N0 M0 | IIIA/B | T3/4 N0 M0 | IIIA | T1-3 N2 M0 |
| IIIB | T4 N0 M0<br>Any T N1 M0 | IIIC | Any T N1 M0 | IIIB | T4 N0-2 M0 |
| IV | Any T any N M1 | IVA<br>IVB | Any T N2 M0<br>Any T any N M1 | IV | Any T any N M1 |

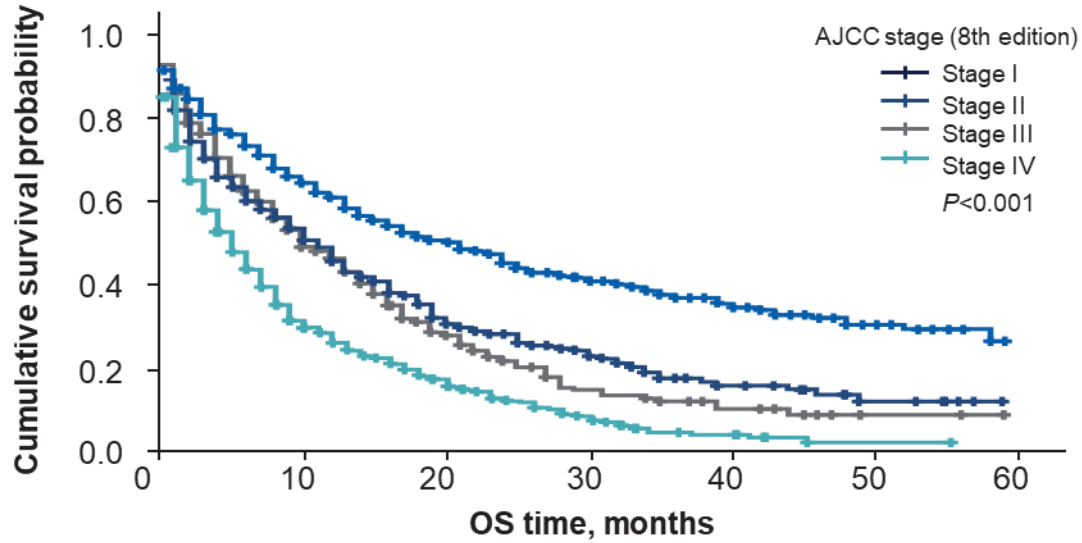
[a] Original source is the *AJCC Cancer Staging Manual,* 8th Edition (2017) published by Springer International Publishing.
AJCC, American Joint Committee on Cancer; Tis, carcinoma in situ; TNM, tumor, node, metastasis.
Liao, et al. *Arch Pathol Lab Med*. 2021 May 1;145(5):543-553.

# 5-Year Survival Rates Among Patients With CCA Remain Poor

## 5-Year Survival by Stage of iCCA (SEER 2012-2018)[1]




## iCCA OS by Stage[2]




**Median OS rates for iCCA**

| Resectable | Unresectable | Stage IV disease |
|---|---|---|
| ≈3 years[3-8] | ≈12-15 months[9-11] | ≈9 months[12] |

Graph reproduced from Meng Z-W, et al. *Oncotarget*. 2017;8(60):101165-101174. Copyright 2017. Licensed under a CC-BY Creative Commons Attribution 3.0 International License (https://creativecommons.org/licenses/by/3.0/).

OS, overall survival.

1. American Cancer Society. Accessed August 2024. https://www.cancer.org/content/dam/CRC/PDF/Public/8554.00.pdf. 2. Meng Z-W, et al. *Oncotarget*. 2017;8:101165-101174. 3. Buettner S, et al. *Onco Targets Ther*. 2017;10:1131-1142. 4. Endo I, et al. *Ann Surg*. 2008;248:84-96. 5. De Jong M, et al. *J Clin Oncol*. 2011;29:3140-3145. 6. Amini N, et al. *J Surg Oncol*. 2014;110:163-170. 7. Koerkamp BG, et al. *J Am Coll Surg*. 2015;221:1041-1049. 8. Chung YJ, et al. *J Korean Surg Soc*. 2013;85:212-218. 9. Schartz DA, et al. *J Vasc Interv Radiol*. 2022;33:679-686. 10. Bridgewater J, et al. *J Hepatol*. 2014;60:1268-1289. 11. Ray CE Jr, et al. *J Vasc Interv Radiol*. 2013;24:1218-1226. 12. Valle J, et al. *N Engl J Med*. 2010;362:1273-1281.

# Genomic Landscape

# Genomic Alterations in CCA May Be Associated With Prognosis

- A prospective study was performed as part of the ICGC and analyzed 489 CCA samples from patients in 10 countries[a]
- Integrative clustering analysis revealed 4 sample clusters which were characterized by different clinical features and genetic, epigenetic, and gene-expression patterns – Cluster 4 is notable as it was comprised of Fluke-Neg, iCCA tumors with FGFR alterations

| Cluster | 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| Genomic alterations | • Highest SNV burden<br>• Enriched in *TP53, ARID1A, BRCA1/2* mutations<br>• Enriched in H3K27 me3-associated promoter mutations | Enriched in *TP53* | | • Enriched in *BAP1* and *IDH1/2* mutations<br>• Enriched in *FGFR* alterations |
| Copy number alterations | *ERBB2* amplification | | ↑ Highest CNA burden 1p, 2p, 2q, 7p, 16p, 19q, 20q | |
| Gene expression | ↑ *ERBB2*<br>↑ TET1 ↓ EZH2 | ↑ CTNNB1, WNT5B, AKT1 | ↑ • Immune-related pathways<br>• *PD-1, PD-L2,* and *BTLA* | ↑ *FGFR1 FGFR2 FGFR3 FGFR4* |
| Methylation phenotype | CpG island hypermethylated | | | CpG shore hypermethylated |
| Prognosis | Poorer prognosis | | | Better prognosis |

**Survival analysis showed improved survival in CCAs of clusters 3 and 4 compared with other clusters**

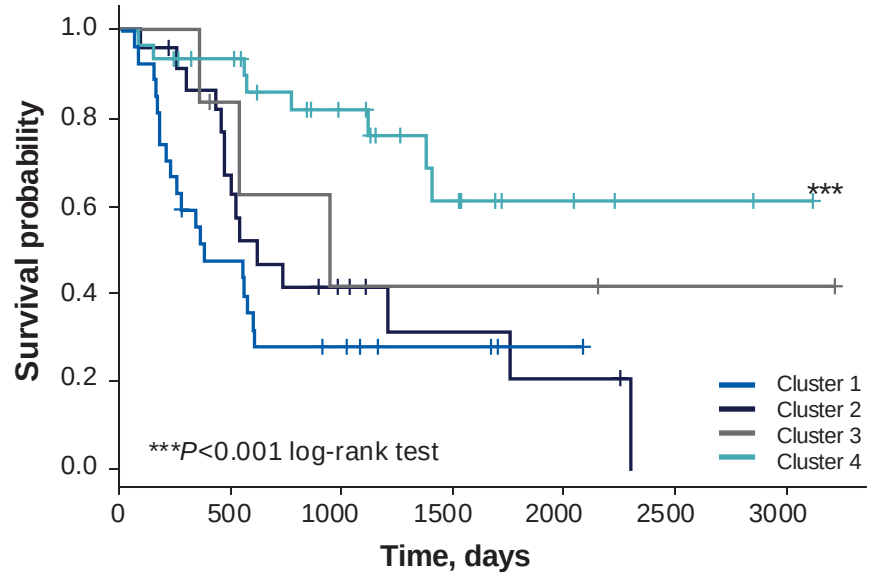



Image Adapted from Cancer Discov, Copyright © 2017, Volume 7/Issue 10, Pages 1116-1135, Jusakul A, et al, Whole-genome and epigenomic landscapes of etiologically distinct subtypes of cholangiocarcinoma, with permission from AACR.

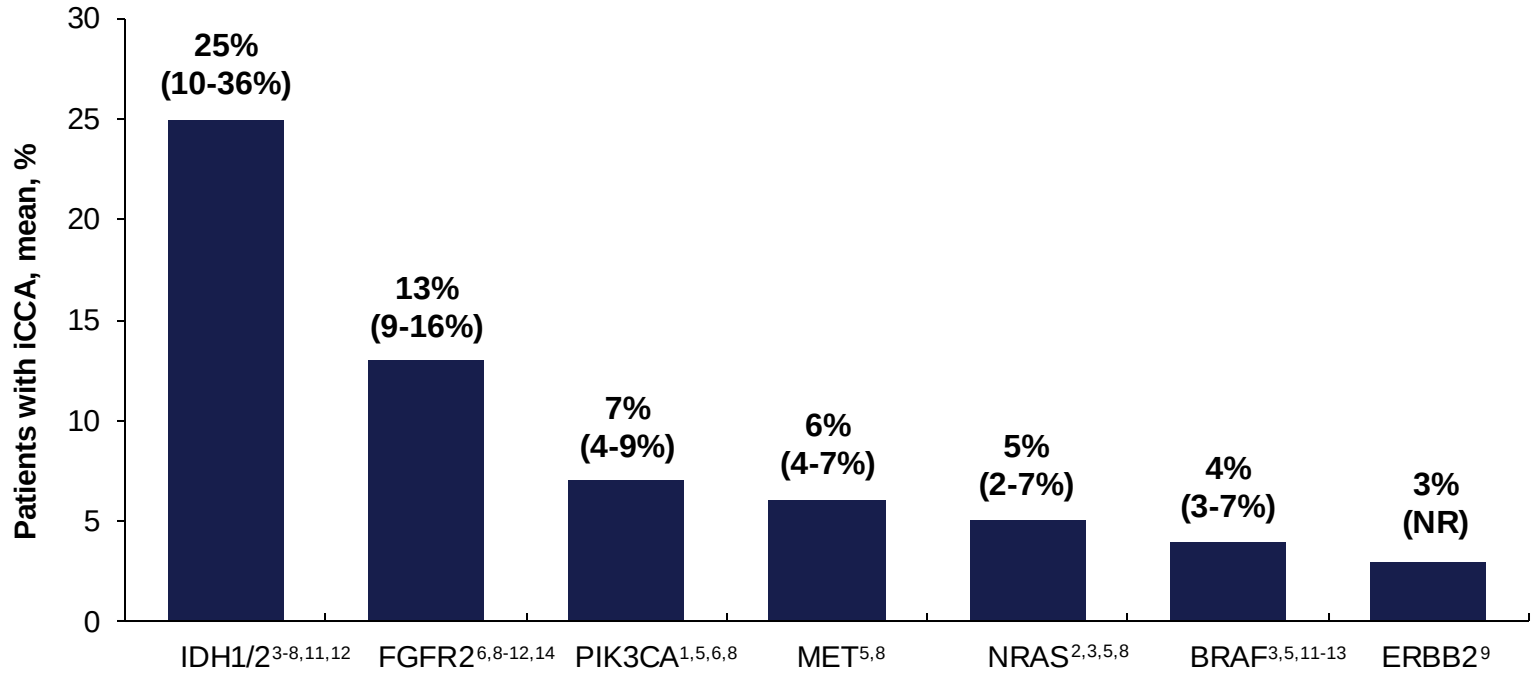
[a] Samples were analyzed using 4 different genomic platforms capable of detecting somatic mutations, somatic copy-number alterations, mRNA expression, and DNA methylation patterns.

BTLA, B and T lymphocyte associated; CNA, copy number alteration; ICGC, International Cancer Genome Consortium; PD1, programmed cell death protein-1; PDL2, programmed cell death ligand 2; SNV, single nucleotide variant.

Jusakul A, et al. *Cancer Discov.* 2017;7:1116-1135.

# Common Alterations in iCCA

## Approximate Incidence (Range) of Common Alterations Targetable With Approved or Late-Stage Experimental Drugs




**Individual studies have reported other potentially oncogenic alterations in iCCA[2-13]**

- *ARAF*
- *ARID1A*
- *BRCA1/2*
- *BAP1*
- *CDKs* (eg, *CDKN2A/B*)
- *EGFR*
- *ERBB2/HER3*
- *KRAS*
- *NF1*
- *TP53*
- *PTEN*
- *ROS1*

**≈50% of iCCAs have genomic alterations that could be used to personalize therapy[8,11,15,16]**

NR, not reported.

1. Riener M-O, et al. *Genes Chromosomes Cancer.* 2008;47:363-367. 2. Deshpande V, et al. *BMC Cancer.* 2011;11:60. 3. Borger DR, et al. *Oncologist.* 2012;17:72-79. 4. Wang P, et al. *Oncogene.* 2013;32:3091-3100. 5. Voss JS, et al. *Hum Path*. 2013;44:1216-1222. 6. Jiao Y, et al. *Nat Genetics.* 2013;45:1470-1473. 7. Chan-On W, et al. *Nat Genetics.* 2013;45:1474-1478. 8. Ross JS, et al. *Oncologist.* 2014;19:235-242. 9. Graham RP, et al. *Hum Pathol*. 2014;45:1630-1638. 10. Arai Y, et al. *Hepatololgy.* 2014;59:1427-1434. 11. Sia D, et al. *Nat Commun.* 2015;6:6087. 12. Javle M, et al. *Cancer.* 2016;122:3838-3847. 13. Sia D, et al. *Gastroenterology*. 2013;144:829-840. 14. Krook MA, et al. *J Clin Oncol.* 2020;15(suppl):3620. 15. Lowery MA, et al. *Clin Cancer Res*. 2018;24:4154-4161. 16. Chun SY, Javle M. *Cancer Contr*. 2017;24:1-7.

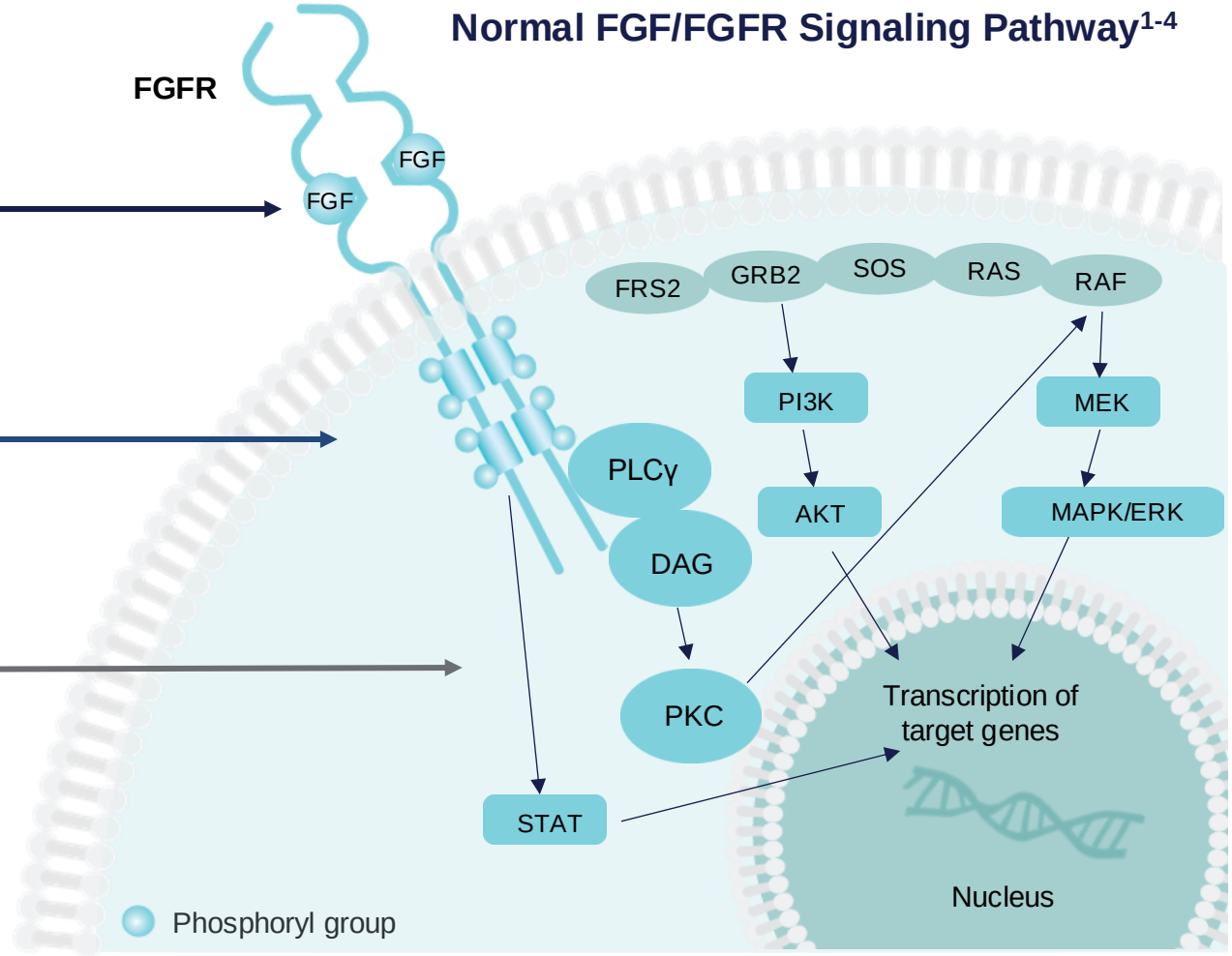
# The FGF/FGFR Signaling Pathway Plays a Central Role in Multiple Cellular Processes[1-4]

Binding of FGF ligands (FGF1 to 23) to their cognate FGF receptors (FGFR1 to 4) leads to receptor dimerization[1,2]

Receptor dimerization induces cross-phosphorylation and activation of the FGFR kinases[1-3]

FGFR kinases activate downstream signaling pathways implicated in cellular processes such as proliferation, survival, migration, and angiogenesis[1,2]

## Normal FGF/FGFR Signaling Pathway[1-4]



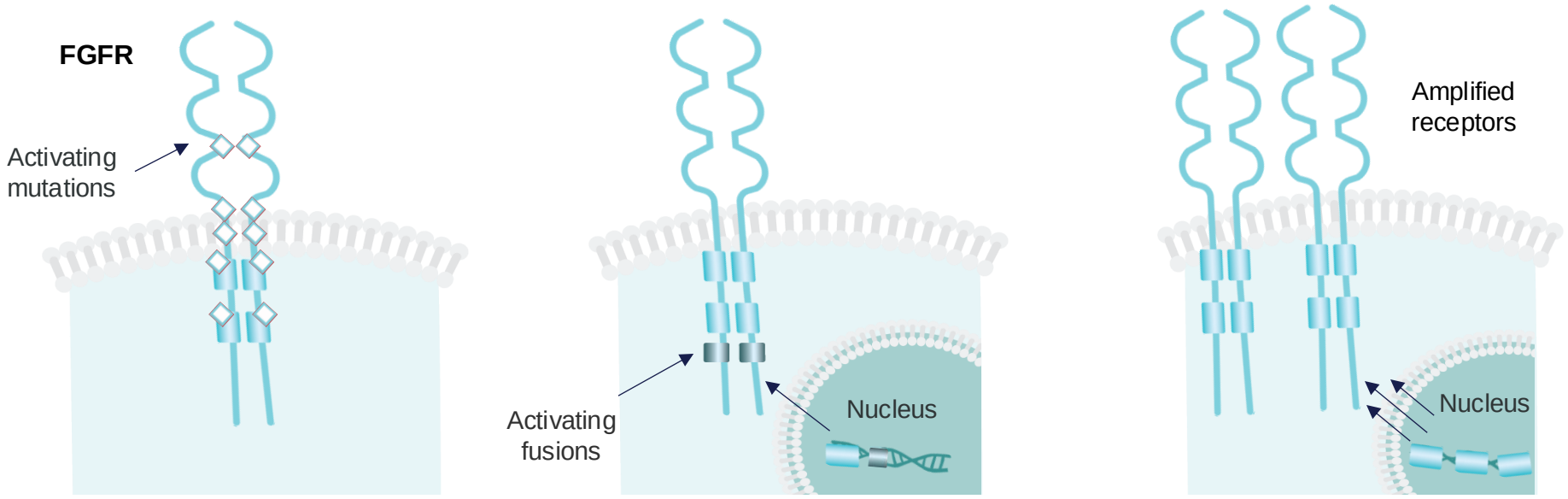

AKT, protein kinase B; DAG, diacylglycerol; ERK, extracellular signal-regulated kinase; FGF, fibroblast growth factor; FRS2, fibroblast growth factor receptor substrate 2; GRB2, growth factor receptor-bound protein 2; MAPK, mitogen-activated protein kinase; MEK, mitogen-activated protein kinase kinase; PI3K, phosphatidylinositol 3-kinase; PKC, protein kinase C; PLCγ, phospholipase C-gamma; RAF, rapidly accelerated fibrosarcoma kinase; RAS, rat sarcoma GTPase; SOS, son of sevenless; STAT, signal transducer and activator of transcription.

1. Babina IS, Turner NC. *Nat Rev Cancer*. 2017;17:318-332. 2. Turner N, Grose R. *Nat Rev Cancer*. 2010;10:116-129. 3. Sarabipour S, Hristova K. *Nat Commun*. 2016;7:10262. 4. Touat M, et al. *Clin Cancer Res*. 2015;21:2684-2694.

# Deregulation of FGFR Signaling Is Implicated in Tumorigenesis

- Aberrant FGFR signaling mediates tumorigenesis by enhancing proliferation, migration, survival, invasion, and angiogenesis[1,2]
- Different genomic alterations may result in tumorigenic FGFR signaling[1]

| Activating Mutations | Chromosomal Rearrangements | Gene Amplifications |
|---|---|---|
| Leading to constitutive activation of the kinase domain or ligand-independent receptor dimerization | Translocations resulting in gene fusions that allow ligand-independent receptor dimerization | Inducing protein overexpression, receptor accumulation and activation of downstream signaling pathways |



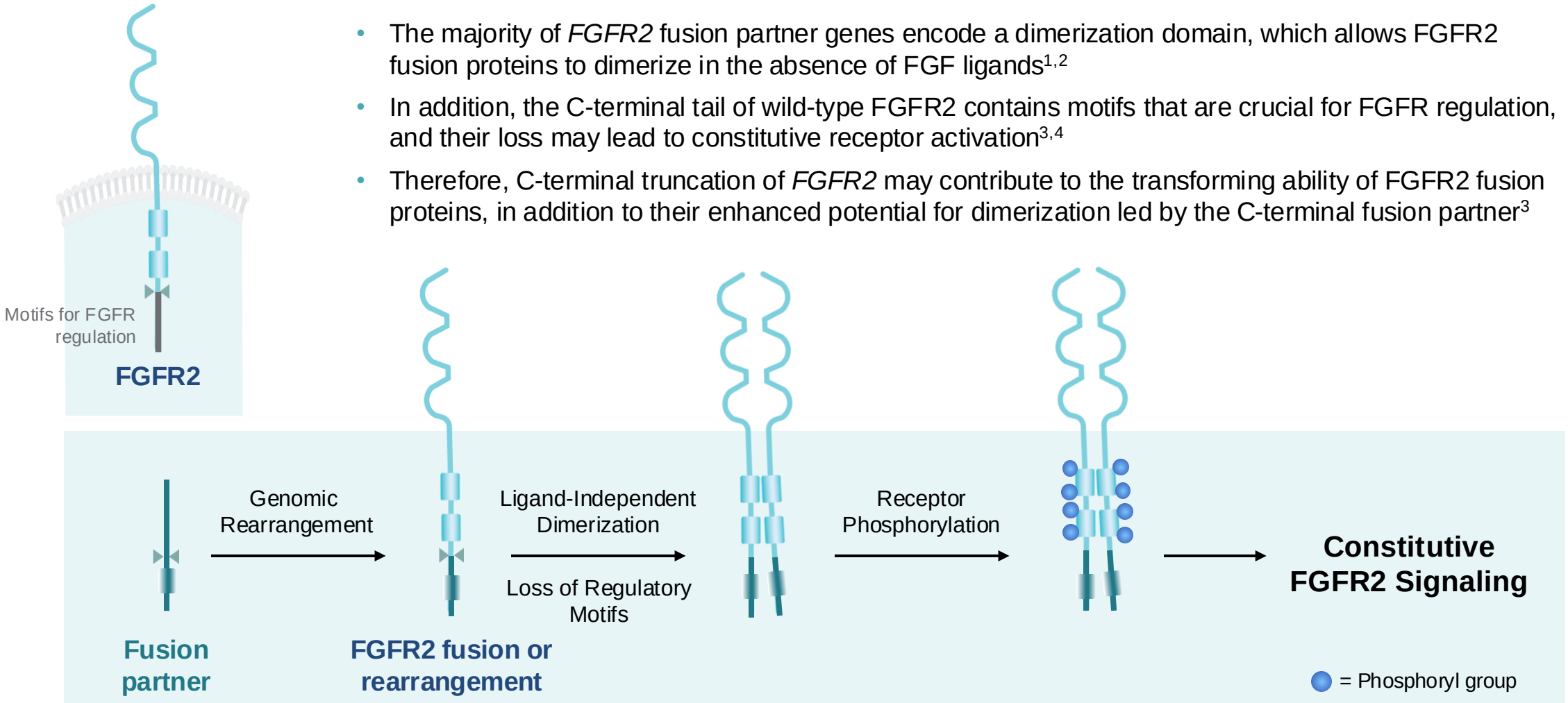

**_FGFR2_ Gene Fusions:**

- Occur in 9-16% of patients with iCCA[3-6]
- Are detected early in disease progression, suggesting that *FGFR2* fusions serve as oncogenic drivers[7]

1. Babina I, Turner N. *Nat Rev Cancer*. 2017;17:318-332. 2. Turner N, Grose R. *Nat Rev Cancer*. 2010;10:116-129. 3. Rizvi S, Borad MJ. *J Gastrointest Oncol*. 2016;7(5):789-796. 4. Graham RP, et al. *Hum Pathol.* 2014;45:1630-1638. 5. Farshidfar F, et al. *Cell Rep*. 2017;18(11):2780-2794. 6. Ross JS, et al. *Oncologist*. 2014;19:235-242. 7. Krook MA, et al. *J Clin Oncol*. 2020;15(suppl):3620.

# *FGFR2* Fusions or Rearrangements May Trigger Ligand-Independent Receptor Dimerization and Constitutive FGFR Signaling, Possibly Driving Tumorigenesis

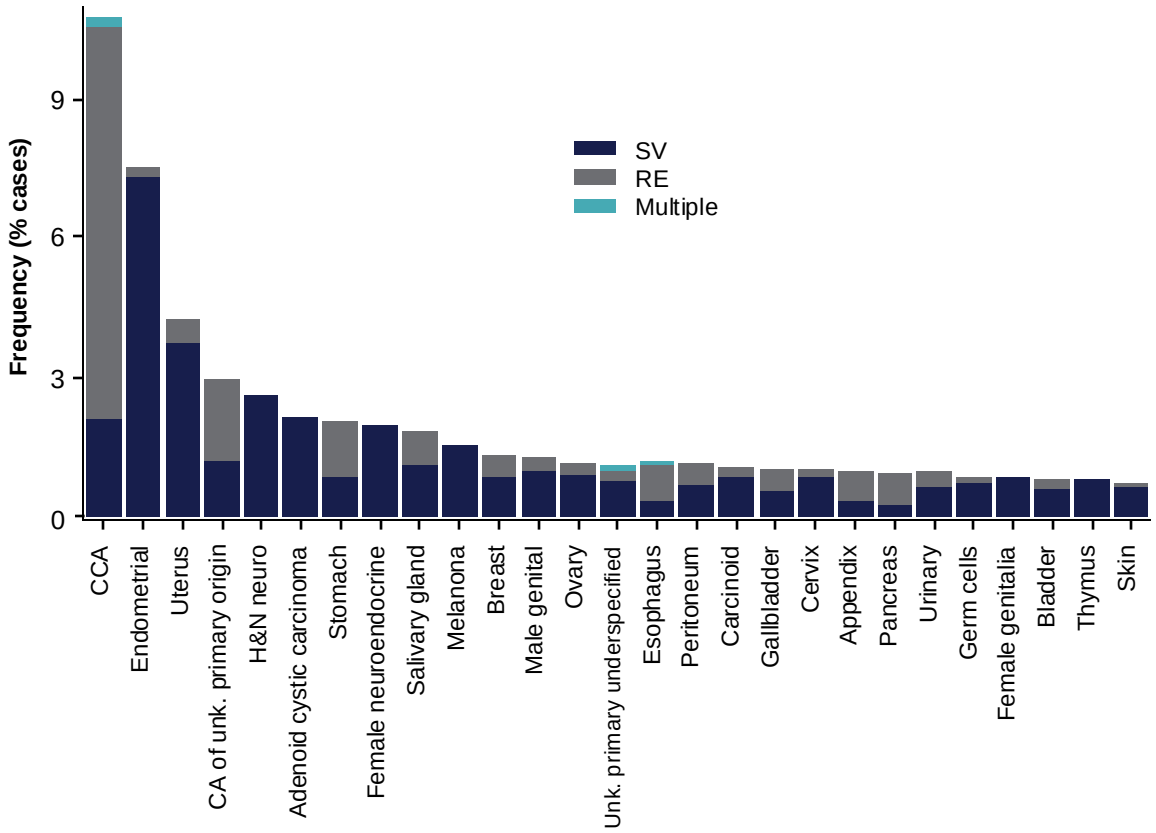
- The majority of *FGFR2* fusion partner genes encode a dimerization domain, which allows FGFR2 fusion proteins to dimerize in the absence of FGF ligands[1,2]
- In addition, the C-terminal tail of wild-type FGFR2 contains motifs that are crucial for FGFR regulation, and their loss may lead to constitutive receptor activation[3,4]
- Therefore, C-terminal truncation of *FGFR2* may contribute to the transforming ability of FGFR2 fusion proteins, in addition to their enhanced potential for dimerization led by the C-terminal fusion partner[3]




1. Gallo LH, et al. *Cytokine Growth Factor Rev*. 2015;26:425-449. 2. Wu YM, et al. *Cancer Discov*. 2013;3:636-647. 3. Li F, et al. *Cytokine Growth Factor Rev*. 2020;52:56-67.
4. Lorenzi MV, et al. *Oncogene*. 1997;15:817-826.

# Oncogenic *FGFR2* Fusions or Rearrangements Are Common Alterations in CCA

## Distribution of *FGFR2* Alterations by Tumor Type[1]




- *FGFR2* genomic alterations were identified in 1.7% of tumor samples from ≈350,000 patients who underwent Foundation Medicine CGP during routine clinical care[1]
- *FGFR2* SVs and rearrangements were most frequently observed in samples from patients with CCA[1]
- Most *FGFR2* alterations in CCA were gene fusions following chromosomal rearrangement[1]
- Other *FGFR2* mutations were also observed in CCA biopsies in this and other studies[1-3]



CA, carcinoma, CGP, comprehensive genomic profiling; H&N, head and neck; RE, rearrangement/fusion; SV, short variant mutation; unk, unknown.

1. Murugesan K, et al. *ESMO Open*. 2022; 6:100641. 2. Javle MM, et al. ASCO 2019. Poster 4087. 3. Silverman IM, et al. *Cancer Discov*. 2021;11:326-339.

# Other Targetable Mutations in iCCA

## *IDH* mutations

- IDH is an essential enzyme for cellular respiration in the TCA cycle[1,2]
- Mutations in *IDH* have been implicated in tumorigenesis, cell maintenance, and proliferation[1,3]

## *BRAF* mutations

- *BRAF* mutations result in constitutive BRAF activation and uncontrolled signaling via the MAPK pathway[4]
  - The MAPK pathway regulates cell signaling from transmembrane growth factor receptors, leading to cell proliferation[5-7]
- *BRAF* mutations have been identified in approximately 5% of patients with CCA, predominantly those with iCCA[8]

BRAF, B-Raf proto-oncogene, serine/threonine kinase; IDH, isocitrate dehydrogenase; TCA, tricarboxylic acid cycle.

1. Fujii T, et al. *Discov Med*. 2016;21:373-380. 2. Presner JR, Chinnaiyan M. *Nat Med.* 2011;17:291-299. 3. Takeishi K, et al. *Cancer Cell.* 2015;28:773-784. 4. Cantwell-Dorris ER, et al. *Mol Cancer Ther.* 2011;10:385-394. 5. Dibb NJ, et al. *Nat Rev Cancer*. 2004;4:718-727. 6. Sánchez-Torres, et al. *Transl Lung Cancer Res.* 2013;2:244-250. 7. Beeram M, et al. *J Clin Oncol*. 2005;23:6771-6790. 8. Silverman IM, et al. ASCO 2019 abstract 4080.

# Key Takeaways

# Key Takeaways

- CCA is a rare malignancy of the biliary tract occurring both inside (iCCA) and outside (eCCA) the liver; despite its rare occurrence, the overall incidence of iCCA has increased in recent years[1,2]
- Diagnosis remains a challenge due to a lack of symptoms and known risk factors for most patients, limited value of tumor markers, and overlap with other disease states (eg, pancreatic cancer, PSC)[3]
- Approximately 30% of patients with a diagnosis of iCCA have resectable disease, yet more than half of patients who undergo resection will experience a relapse[4,5]
  - Prognosis for patients with a diagnosis of CCA remains poor, with median survival rates in resectable and unresectable disease of ≈3 years and 12-15 months, respectively[4,6-8]
- Genomic analyses of CCA tumors have identified actionable oncogenic mutations[9]
  - Alterations in *FGFR* and *IDH* have been identified in ≈9-16% and ≈ 25% of patients with iCCA, respectively[9-15]

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