# Biliary tract consensus cancer subtypes improve outcome stratification over anatomy

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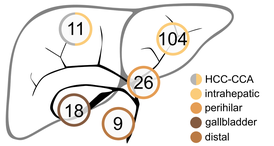
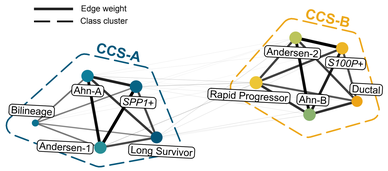
## Background

Biliary tract cancers (BTC) groups a molecularly heterogeneous family of diseases based on shared anatomy and joint clinical care. Several molecular classification systems based on RNA demonstrate prognostic relevance, however clinical implementation has been limited by a lack of consensus or elucidation of the biological underpinnings of the classes.

## Methods

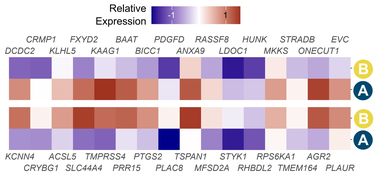
We performed whole genome transcriptome sequencing on **169** biliary tract tumors, enriched by laser capture microdissection, and annotated with clinical data.

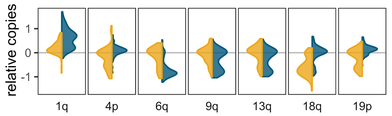



Assigning samples to existing RNA-based classes and visualizing as a network, we observed that several classifiers overlap. Clustering on the network, we define two consensus cancer subtypes (**A** and **B**).

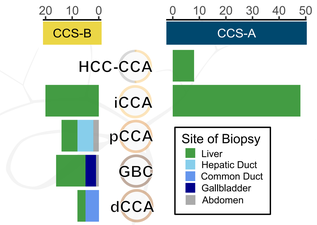
With samples assigned to each cluster, we trained a top scoring pair algorithm that could predict the subtype of a specimen from bulk RNA with an accuracy of 1 [.82-1]




A genetic model, trained on chromosome arm copies, was able to reach an AUC of .87.

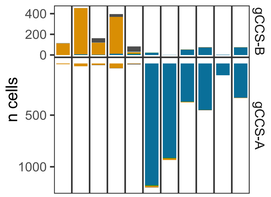
## Results

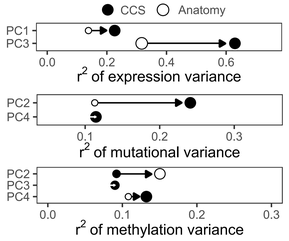



Classifying bulk tumor specimen by subtype showed strong spatial segregation along the biliary tract. For a given case, subtype assignment did not change in metastasis nor recurrence.

In single cell RNAseq data[1], gene expression programmes associated with each subtypes could be confidently assigned to cells with the matching chromosome-arm copy-number profiles.

[1]Song, G. et al. (2022) *Nat. Comms.* 13, 1642.

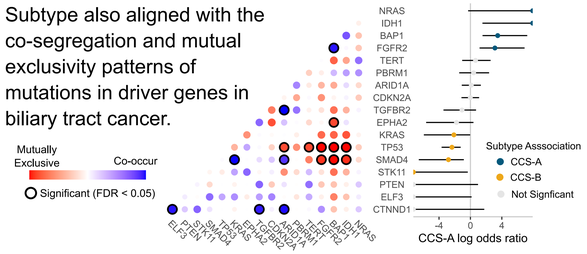



Subtype explained more molecular variance than anatomical site of the primary tumor across gene expression data, mutational signatures, and public methylation data[2].

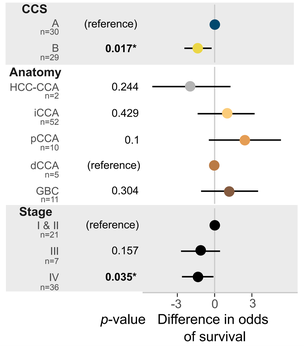
[2]Jusakul, A. (2017) *Cancer Disc.* 7, 1116–1135.

Subtype also aligned with the co-segregation and mutual exclusivity patterns of mutations in driver genes in biliary tract cancer.




## Results ctn'd

Subtype better explained outcome than anatomical location in the surgical ($P$ = 0.005) and advanced (see figure) settings. Neither the prognostic significance of genetic drivers nor survival improvements from precision therapies (e.g. IDH- or FGFR-inhibitors) could account for this survival difference.




## Conclusion

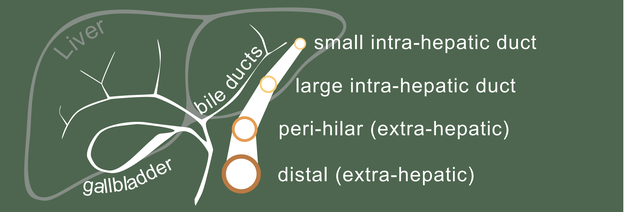
Consensus cancer subtypes of biliary tract cancer define two molecular lineages that improve biological and clinical stratification over anatomy.

## Acknowledgments

We thank patients and caregivers, the Richard Legresley Biliary Cancer Research Fund through the Princess Margaret Cancer Foundation, and the TFRI Marathon of Hope Cancer Centers Network. We share these findings with respect for everyone affected by this disease and with the goal of improving understanding, care, and outcomes for patients and families.

## Patient Friendly Summary

The bile ducts are a continuous system of tubes, increasing in size from the liver to where they connect to the intestine. Because what ducts do changes as they get largers, their cancers have different effects on our health. Based on how bile ducts look (their anatomy), bile duct cancers can be split into several anatomical types:




Because many new cancer treatments use molecular targets, we asked: ***how many molecular types of bile duct cancers are there?***

We took our database of 169 biliary tract tumors and checked what types they were using molecular types defined in previous studies. We found ***most studies agree to assign biliary tract tumors to two molecular types***.

We called them type **A** and **B**.

The types seperate strongly by their location in the biliary tract: we find ***the molecular profiles of tumors from small bile ducts inside of the liver are very different from all other biliary tract tumors.***

We found that ***people with A-type tumors lived longer on average than people with B-type tumors***, which could impact the choices of patients and their care teams. This difference reflects trends seen across many patients and does not predict what will happen for any one individual. We are now working with other institutions to understand if these molecular types also have treatment-choice implications.