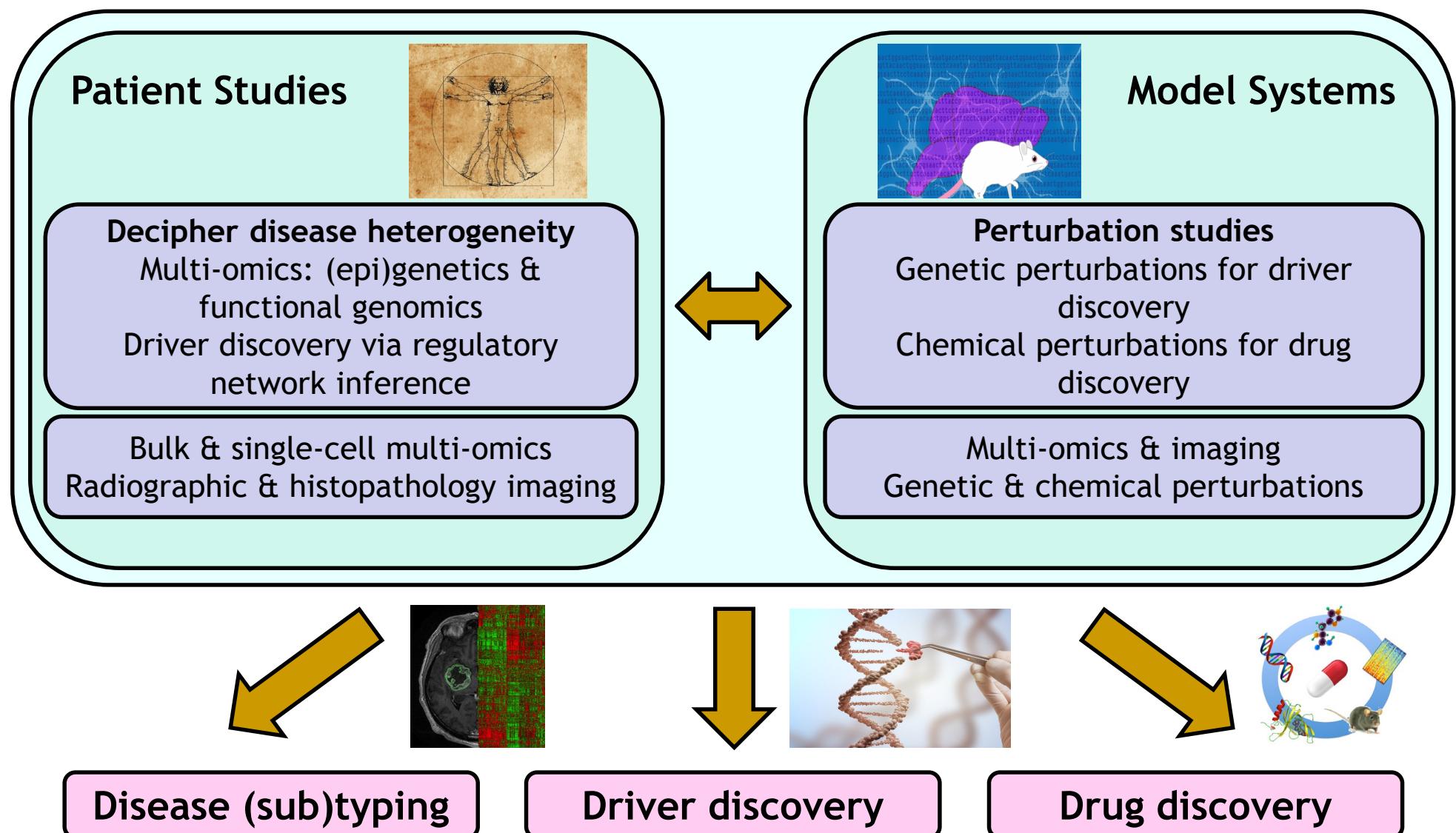


*AMARETTO framework: A data-driven platform based on multimodal and multiscale network inference for diagnostic, prognostic and therapeutic decision-making in cancer

The *AMARETTO framework learns networks of regulatory circuits - circuits of target genes and their shared drivers - across biological systems with applications from disease subtyping to driver and drug discovery in cancer.

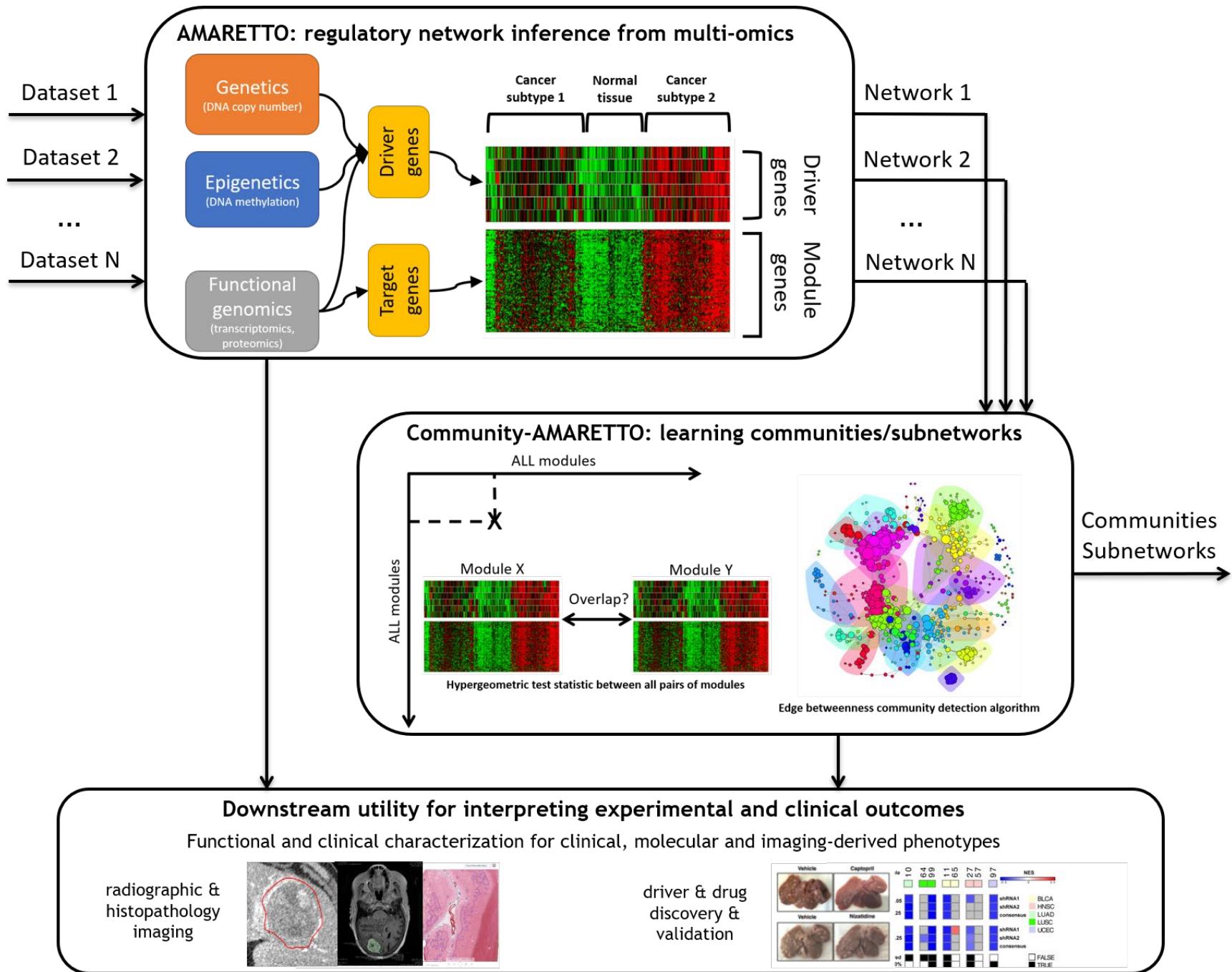


The *AMARETTO framework features:

- (1) Modular approach to incorporating prior biological knowledge.
- (2) Downstream utility of circuits for interpreting experimental and clinical outcomes.
- (3) Multimodal and multiscale inference of regulatory circuits in cancer.

AMARETTO & Community-AMARETTO

Multimodal and multiscale data fusion for diagnostics, prognostics and therapeutics in cancer



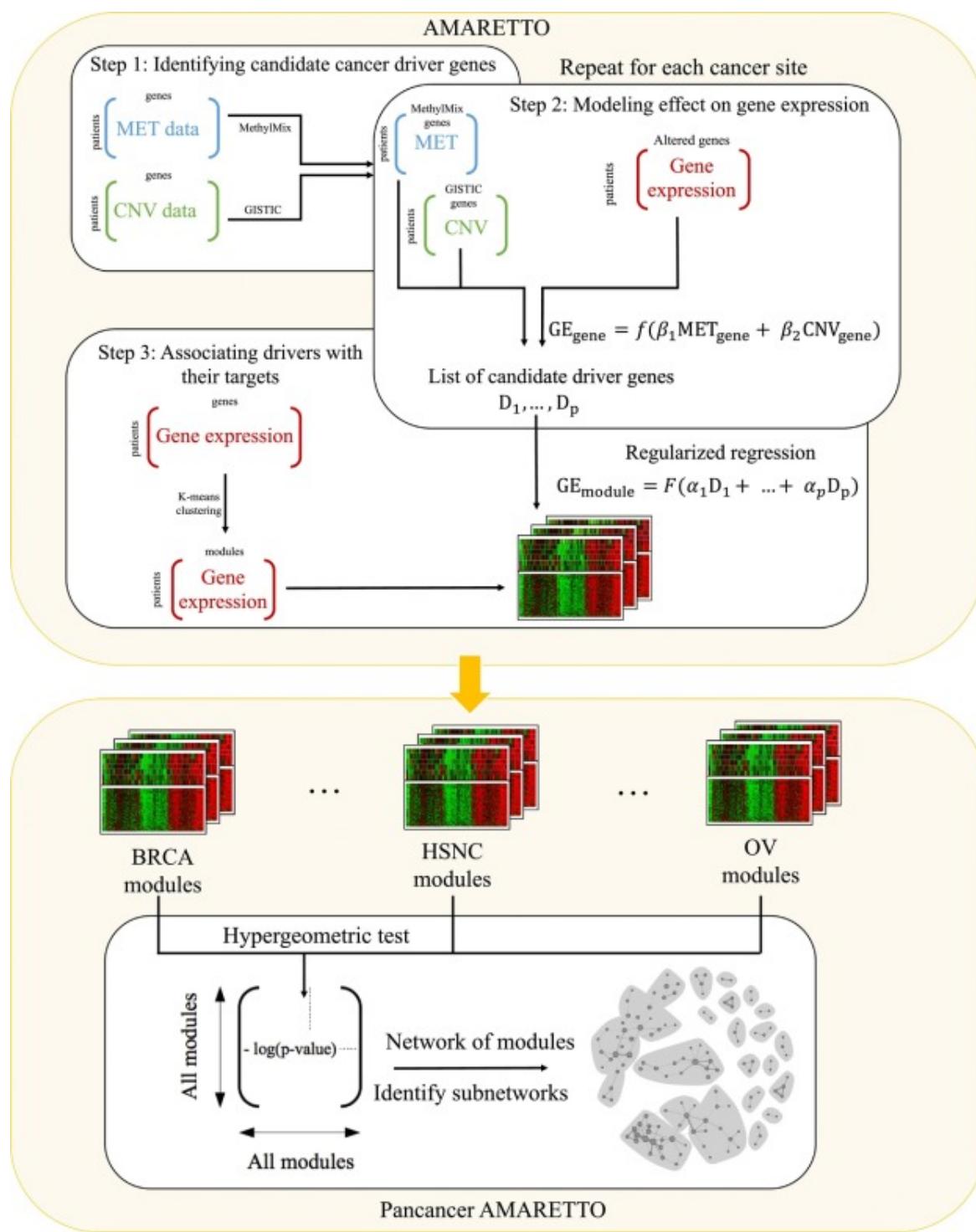
Core algorithms yield multimodal and multiscale reformulations to network inference:

1. The **AMARETTO** algorithm infers regulatory circuits within each biological system (e.g., within diseases, individuals and cohorts, model systems and patient studies, *in vitro* and *in vivo* systems) from functional genomics or multi-omics data;
2. The **Community-AMARETTO** algorithm identifies subnetworks of regulatory circuits shared and distinct across biological systems (e.g., across diseases, individuals and cohorts, model systems and patient studies, *in vitro* and *in vivo* systems);
3. The **Perturbation-AMARETTO** algorithm provides enhanced reformulations for simultaneous driver and drug discovery; each accompanied by tools for optimizing generalized prediction performances.

Downstream utility of circuits for interpreting experimental and clinical outcomes:

1. Functional characterization in known functional categories;
2. Clinical characterization for clinical, molecular and imaging-derived phenotypes;
3. Prioritization and validation of drivers using genetic perturbations;
4. Discovering drug treatments modulating drivers and targets using chemical perturbations.

Pancancer AMARETTO: Pan-cancer driver discovery using AMARETTO & Community-AMARETTO



Workflow of *AMARETTO:

First, AMARETTO infers regulatory networks within each biological system via multi-omics data fusion. Specifically, AMARETTO identifies potential cancer drivers by identifying genes whose genetic and epigenetic cancer aberrations have a direct functional impact on their own transcriptomic or proteomic expression. AMARETTO then connects these drivers with modules of co-expressed target genes that they putatively control, defined as regulatory circuits, using a penalized regulatory program. Second, Community-AMARETTO learns communities or subnetworks by connecting the regulatory circuits inferred from different systems to identify drivers across diseases or biological systems.

Applications: Multimodal and Multiscale Inference in Cancer

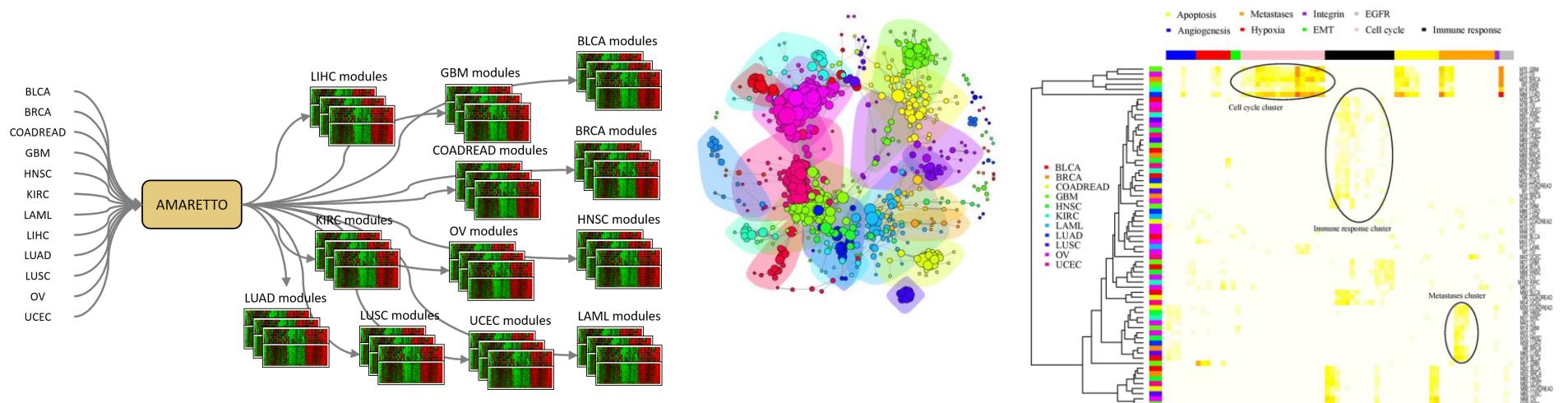
1. Pan-cancer driver discovery

Driver prediction for pan-cancer multi-omics subnetworks across 12 cancer (sub)types
validated using genetic perturbations in cell lines

Drivers of smoking-induced cancer and
'antiviral' interferon-modulated
innate immune response across 12
cancer (sub)types

Pan-cancer
communities or
subnetworks

Pan-cancer functional
categories
⇒ AMARETTO captures
hallmarks of cancer

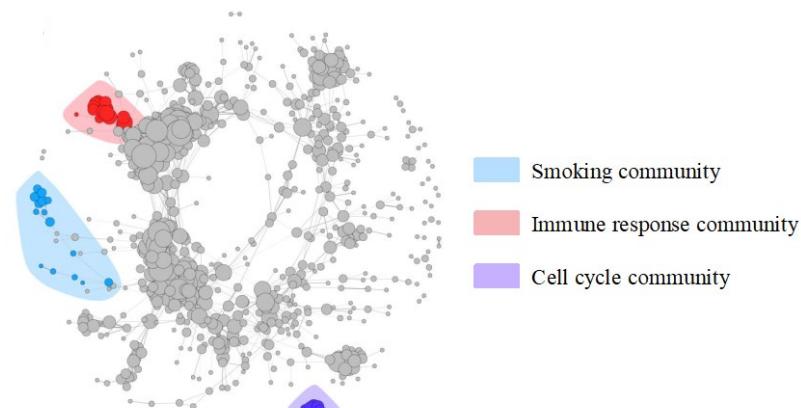


Driver discovery:

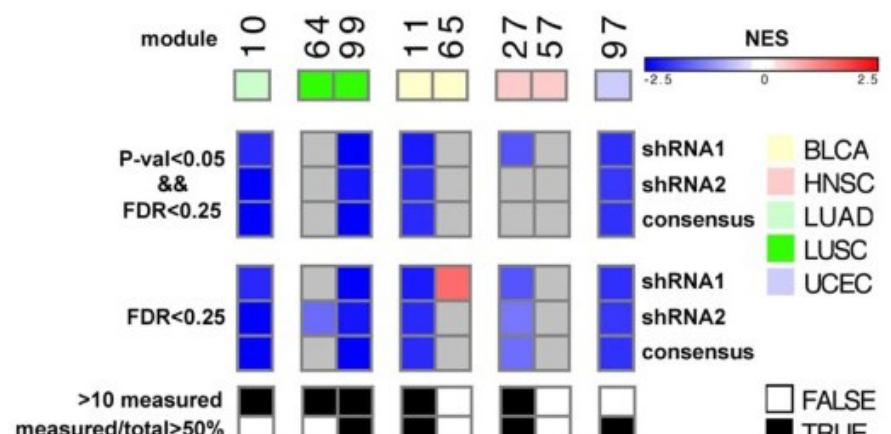
- OAS2 pan-cancer driver of 'antiviral' interferon-modulated innate immune response
- GPX2 pan-cancer driver of smoking-induced cancer

Driver validation:

Genetic perturbations of GPX2 in the
A549 (LUAD) cell line
⇒ Knocking down GPX2 represses
target genes in GPX2-regulated circuits



Nathalie Pochet and Olivier Gevaert, *EBioMedicine* 2018



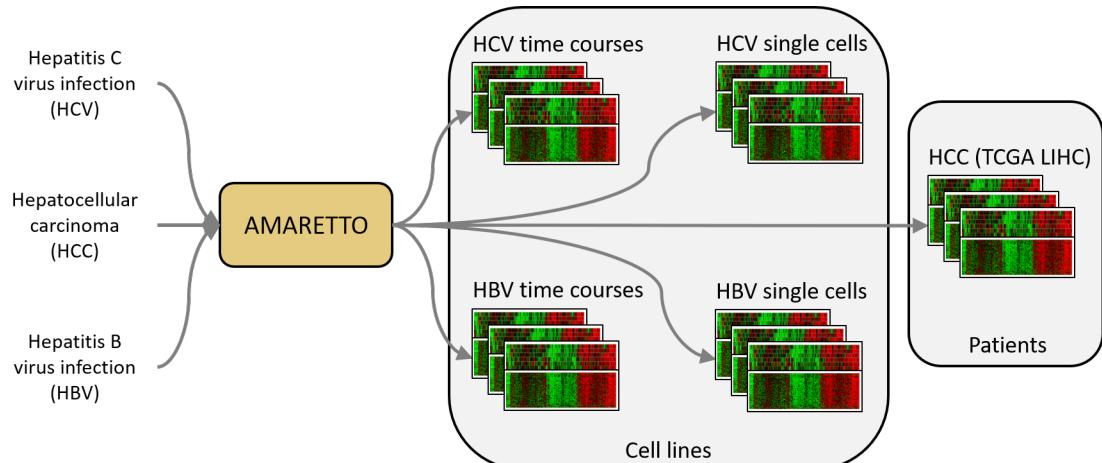
Drivers of smoking-induced cancer and 'antiviral' interferon-modulated
innate immune response across 12 cancer (sub)types (GBM, LIHC)
⇒ AMARETTO facilitates identification of known and novel cancer
drivers and their targets

Applications: Multimodal and Multiscale Inference in Cancer

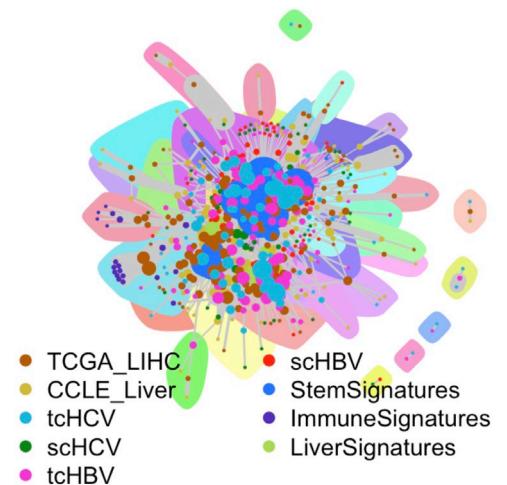
2. Studying virus-induced hepatocellular carcinoma

Driver prediction for hepatitis C and B virus-induced hepatocellular carcinoma across subnetworks derived from >6 systems validated in cell lines, and prediction of chemopreventive treatments modulating disease-associated subnetworks using chemical perturbations in cell lines, experimentally validated in rat models

Driver and drug discovery for hepatitis C (HCV) and hepatitis B (HBV) virus-induced hepatocellular carcinoma (HCC)



Pan-etiology of cancer communities or subnetworks



Drug discovery:

Chemical perturbations in cell lines

Predict which drug compounds can reverse disease-associated circuits

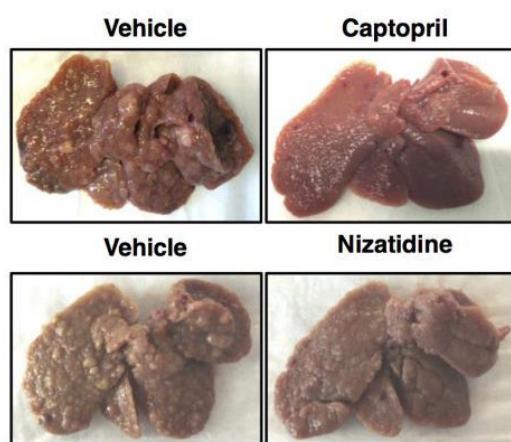
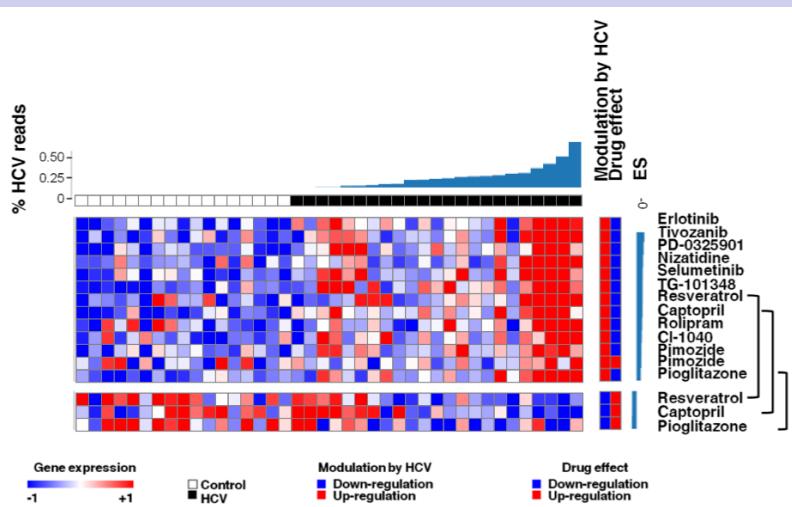
Alternative treatments with less severe adverse effects?

Drug validation:

Experimental validation of drugs in rat models

⇒ Two novel compounds attenuate HCC development

⇒ Safe and low-cost approach for chemoprevention of HCC?



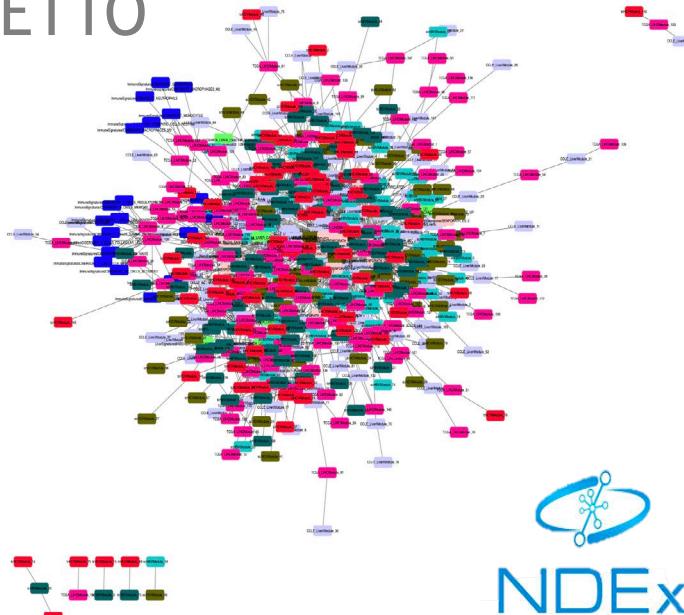
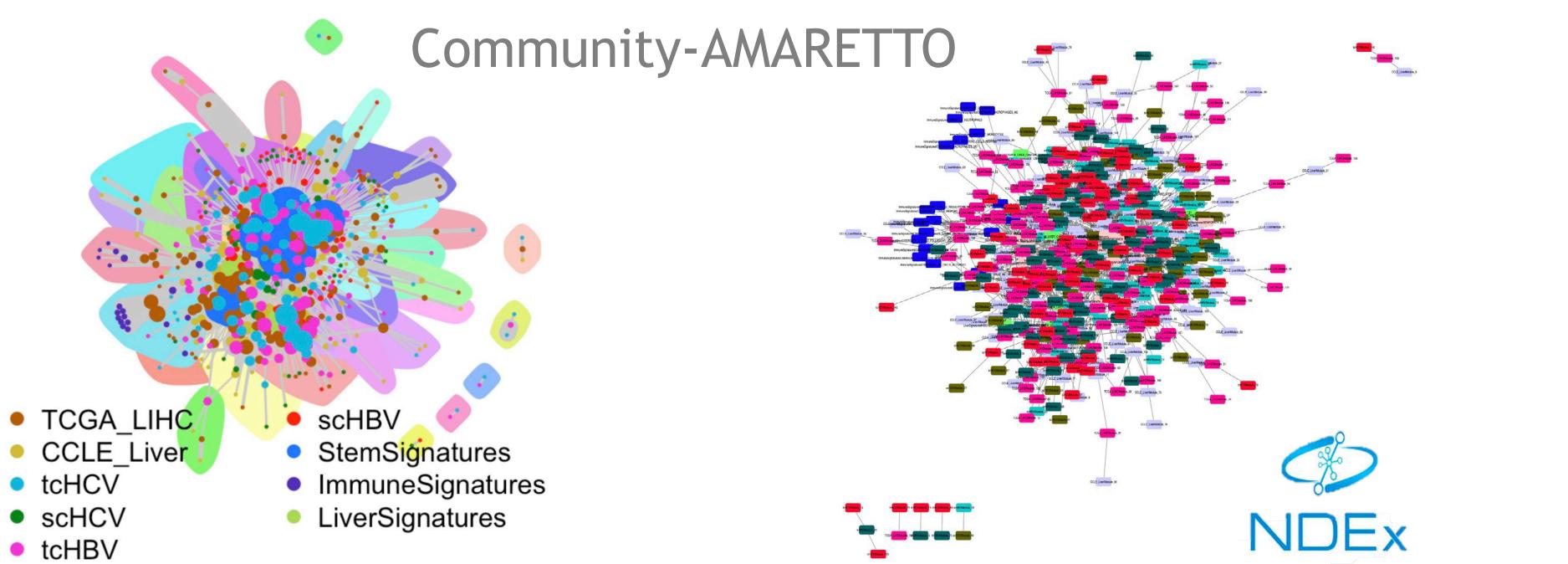
Nathalie Pochet and Thomas Baumert, submitted

Driver and drug discovery for chemoprevention of hepatitis C (HCV) and hepatitis B (HBV) virus-induced hepatocellular carcinoma (HCC)
 ⇒ AMARETTO facilitates identification of known and novel drug compounds and how they modulate cancer drivers and their targets

Applications: Multimodal and Multiscale Inference in Cancer

2. Studying virus-induced hepatocellular carcinoma

Community-AMARETTO



Community	CCLE_Liver	scHBV	scHCV	TCGA_LIHC	tcHBV	tcHCV	ImmuneSignatures	LiverSignatures	StemSignatures																																																															
Community 1	Module 4, Module 5, Module 10, Module 12, Module 20, Module 21, Module 27, Module 32, Module 33, Module 41, Module 47, Module 50, Module 57, Module 58, Module 61, Module 85, Module 90, Module 95, Module 98, Module 111, Module 113, Module 117, Module 119, Module 126, Module 127, Module 137, Module 140, Module 142, Module 148	Module 1, Module 2, Module 3, Module 4, Module 5, Module 10, Module 11, Module 12, Module 20, Module 22, Module 25, Module 26, Module 27, Module 28, Module 30, Module 37, Module 39, Module 40, Module 44, Module 48, Module 50, Module 54, Module 55, Module 58, Module 60, Module 62, Module 72, Module 74, Module 80, Module 83, Module 85, Module 93, Module 99, Module 100	Module 3, Module 5, Module 10, Module 13, Module 14, Module 25, Module 30, Module 33, Module 37, Module 45, Module 48, Module 55, Module 58, Module 59, Module 74, Module 77, Module 79, Module 80, Module 81, Module 88, Module 89, Module 97, Module 113, Module 115, Module 118, Module 118, Module 123, Module 124, Module 125, Module 128, Module 139, Module 141, Module 145	Module 11, Module 38, Module 50, Module 59, Module 67, Module 79, Module 89, Module 102, Module 123, Module 150	Module 35, Module 42, Module 43, Module 47, Module 59, Module 115, Module 122, Module 130, Module 145	CIBERSORT_MAST_CELLS_RESTING	HOSHIDA_LIVER_CANCER_SUBCLASS_S1, HOSHIDA_LIVER_CANCER_SURVIVAL_UP	BENPORATH_EED_TARGETS, BENPORATH_ES_WITH_H3K27ME3, BENPORATH_PRC2_TARGETS, BENPORATH_SUZ12_TARGETS	 Community 1																																																															
<ul style="list-style-type: none"> ➤ Genes from 'subtype S1' signature of hepatocellular carcinoma (HCC): aberrant activation of the WNT signaling pathway ➤ Survival signature genes defined in adjacent liver tissue: genes correlated with poor survival of hepatocellular carcinoma (HCC) patients ➤ Polycomb Repression Complex 2 (PRC) targets; identified by ChIP on chip on human embryonic stem cells as genes that: possess the trimethylated H3K27 mark in their promoters and are bound by SUZ12 and EED Polycomb proteins ➤ IL8 pan-etiology driver of HCV and HBV virus-induced HCC associated with HCV and HBV viral load and HCC survival 																																																																								
<table border="1"> <thead> <tr> <th>Community</th><th>CCLE_Liver</th><th>scHBV</th><th>scHCV</th><th>TCGA_LIHC</th><th>tcHBV</th><th>tcHCV</th><th>ImmuneSignatures</th><th>LiverSignatures</th><th>StemSignatures</th></tr> </thead> <tbody> <tr> <td>Community 3</td><td>Module 4, Module 5, Module 10, Module 12, Module 20, Module 21, Module 27, Module 32, Module 33, Module 41, Module 47, Module 50, Module 57, Module 58, Module 61, Module 85, Module 90, Module 95, Module 98, Module 111, Module 113, Module 117, Module 119, Module 126, Module 127, Module 137, Module 140, Module 142, Module 148</td><td>Module 1, Module 2, Module 3, Module 4, Module 5, Module 10, Module 11, Module 12, Module 20, Module 22, Module 25, Module 26, Module 27, Module 28, Module 30, Module 37, Module 39, Module 40, Module 44, Module 48, Module 50, Module 54, Module 55, Module 58, Module 60, Module 62, Module 72, Module 74, Module 80, Module 83, Module 85, Module 93, Module 99, Module 100</td><td>Module 2, Module 5, Module 6, Module 10, Module 11, Module 18, Module 25, Module 34, Module 45, Module 48, Module 49, Module 51, Module 52, Module 53, Module 60, Module 61, Module 62, Module 65, Module 67, Module 74, Module 77, Module 79, Module 80, Module 84, Module 86, Module 87, Module 90, Module 92, Module 98, Module 104, Module 111, Module 118, Module 121, Module 125, Module 143, Module 144, Module 149</td><td>Module 14, Module 15, Module 30, Module 40, Module 51, Module 65, Module 70, Module 82, Module 92, Module 107, Module 111, Module 118, Module 121, Module 125, Module 143, Module 144, Module 149</td><td>Module 6, Module 19, Module 27, Module 52, Module 54, Module 71, Module 82, Module 88, Module 97, Module 99, Module 111, Module 120, Module 129</td><td>0</td><td>HOSHIDA_LIVER_CANCER_SUBCLASS_S2</td><td>BENPORATH_MYC_MAX_TARGETS, BENPORATH_MYC_TARGETS_WITH_EBOX, BENPORATH_NANOG_TARGETS, BENPORATH_OCT4_TARGETS, BENPORATH_SOX2_TARGETS</td><td colspan="2"> Community 3 </td></tr> <tr> <td colspan="10"> <ul style="list-style-type: none"> ➤ Genes from 'subtype S2' signature of hepatocellular carcinoma (HCC): proliferation, MYC and AKT1 activation ➤ MYC targets; targets of c-Myc and Max identified by ChIP on chip in a Burkitt's lymphoma cell line; overlap set; and in cultured cell lines, focusing on E-box-containing genes; high affinity bound subset ➤ CORE stemness genes upregulated and identified by ChIP on chip as NOS (Nanog, OCT4, SOX2) transcription factor targets in human embryonic stem cells ➤ STX7 pan-etiology driver of HCV and HBV virus-induced HCC </td></tr> <tr> <td colspan="10"> <table border="1"> <thead> <tr> <th>Community</th><th>CCLE_Liver</th><th>scHBV</th><th>scHCV</th><th>TCGA_LIHC</th><th>tcHBV</th><th>tcHCV</th><th>ImmuneSignatures</th><th>LiverSignatures</th><th>StemSignatures</th></tr> </thead> <tbody> <tr> <td>Community 5</td><td>Module 8, Module 55, Module 67, Module 71, Module 72, Module 77, Module 81, Module 92, Module 121, Module 124, Module 145, Module 150</td><td>Module 23, Module 29, Module 33, Module 71, Module 81, Module 82</td><td>Module 8, Module 24, Module 41, Module 83, Module 83, Module 97</td><td>Module 12, Module 22, Module 24, Module 36, Module 42, Module 51, Module 53, Module 63, Module 64, Module 70, Module 75, Module 85, Module 92, Module 110, Module 117, Module 120, Module 128, Module 142</td><td>Module 10, Module 45, Module 48, Module 83, Module 97, Module 109, Module 128, Module 129, Module 137, Module 138, Module 139, Module 145</td><td>Module 8, Module 57, Module 58, Module 74, Module 79, Module 83, Module 96</td><td>HOSHIDA_LIVER_CANCER_LATE_RECURRENCE_DN, HOSHIDA_LIVER_CANCER_SUBCLASS_S3, HOSHIDA_LIVER_CANCER_SURVIVAL_DN</td><td>0</td><td colspan="2"> Community 5 </td></tr> <tr> <td colspan="10"> <ul style="list-style-type: none"> ➤ Genes from 'subtype S3' signature of hepatocellular carcinoma (HCC): hepatocyte differentiation ➤ Survival signature genes defined in adjacent liver tissue: genes correlated with good survival of hepatocellular carcinoma (HCC) patients ➤ Liver specific genes from Human Gene Expression Index, the HuGE Index, http://www.hugeindex.org ➤ APOC3 pan-etiology driver of HCV and HBV virus-induced HCC validated in all 6 data sources using genetic perturbations of APOC3 in the HepG2 liver cancer cell line </td></tr> </tbody> </table> </td></tr> </tbody> </table>	Community	CCLE_Liver	scHBV	scHCV	TCGA_LIHC	tcHBV	tcHCV	ImmuneSignatures	LiverSignatures	StemSignatures	Community 3	Module 4, Module 5, Module 10, Module 12, Module 20, Module 21, Module 27, Module 32, Module 33, Module 41, Module 47, Module 50, Module 57, Module 58, Module 61, Module 85, Module 90, Module 95, Module 98, Module 111, Module 113, Module 117, Module 119, Module 126, Module 127, Module 137, Module 140, Module 142, Module 148	Module 1, Module 2, Module 3, Module 4, Module 5, Module 10, Module 11, Module 12, Module 20, Module 22, Module 25, Module 26, Module 27, Module 28, Module 30, Module 37, Module 39, Module 40, Module 44, Module 48, Module 50, Module 54, Module 55, Module 58, Module 60, Module 62, Module 72, Module 74, Module 80, Module 83, Module 85, Module 93, Module 99, Module 100	Module 2, Module 5, Module 6, Module 10, Module 11, Module 18, Module 25, Module 34, Module 45, Module 48, Module 49, Module 51, Module 52, Module 53, Module 60, Module 61, Module 62, Module 65, Module 67, Module 74, Module 77, Module 79, Module 80, Module 84, Module 86, Module 87, Module 90, Module 92, Module 98, Module 104, Module 111, Module 118, Module 121, Module 125, Module 143, Module 144, Module 149	Module 14, Module 15, Module 30, Module 40, Module 51, Module 65, Module 70, Module 82, Module 92, Module 107, Module 111, Module 118, Module 121, Module 125, Module 143, Module 144, Module 149	Module 6, Module 19, Module 27, Module 52, Module 54, Module 71, Module 82, Module 88, Module 97, Module 99, Module 111, Module 120, Module 129	0	HOSHIDA_LIVER_CANCER_SUBCLASS_S2	BENPORATH_MYC_MAX_TARGETS, BENPORATH_MYC_TARGETS_WITH_EBOX, BENPORATH_NANOG_TARGETS, BENPORATH_OCT4_TARGETS, BENPORATH_SOX2_TARGETS	 Community 3		<ul style="list-style-type: none"> ➤ Genes from 'subtype S2' signature of hepatocellular carcinoma (HCC): proliferation, MYC and AKT1 activation ➤ MYC targets; targets of c-Myc and Max identified by ChIP on chip in a Burkitt's lymphoma cell line; overlap set; and in cultured cell lines, focusing on E-box-containing genes; high affinity bound subset ➤ CORE stemness genes upregulated and identified by ChIP on chip as NOS (Nanog, OCT4, SOX2) transcription factor targets in human embryonic stem cells ➤ STX7 pan-etiology driver of HCV and HBV virus-induced HCC 										<table border="1"> <thead> <tr> <th>Community</th><th>CCLE_Liver</th><th>scHBV</th><th>scHCV</th><th>TCGA_LIHC</th><th>tcHBV</th><th>tcHCV</th><th>ImmuneSignatures</th><th>LiverSignatures</th><th>StemSignatures</th></tr> </thead> <tbody> <tr> <td>Community 5</td><td>Module 8, Module 55, Module 67, Module 71, Module 72, Module 77, Module 81, Module 92, Module 121, Module 124, Module 145, Module 150</td><td>Module 23, Module 29, Module 33, Module 71, Module 81, Module 82</td><td>Module 8, Module 24, Module 41, Module 83, Module 83, Module 97</td><td>Module 12, Module 22, Module 24, Module 36, Module 42, Module 51, Module 53, Module 63, Module 64, Module 70, Module 75, Module 85, Module 92, Module 110, Module 117, Module 120, Module 128, Module 142</td><td>Module 10, Module 45, Module 48, Module 83, Module 97, Module 109, Module 128, Module 129, Module 137, Module 138, Module 139, Module 145</td><td>Module 8, Module 57, Module 58, Module 74, Module 79, Module 83, Module 96</td><td>HOSHIDA_LIVER_CANCER_LATE_RECURRENCE_DN, HOSHIDA_LIVER_CANCER_SUBCLASS_S3, HOSHIDA_LIVER_CANCER_SURVIVAL_DN</td><td>0</td><td colspan="2"> Community 5 </td></tr> <tr> <td colspan="10"> <ul style="list-style-type: none"> ➤ Genes from 'subtype S3' signature of hepatocellular carcinoma (HCC): hepatocyte differentiation ➤ Survival signature genes defined in adjacent liver tissue: genes correlated with good survival of hepatocellular carcinoma (HCC) patients ➤ Liver specific genes from Human Gene Expression Index, the HuGE Index, http://www.hugeindex.org ➤ APOC3 pan-etiology driver of HCV and HBV virus-induced HCC validated in all 6 data sources using genetic perturbations of APOC3 in the HepG2 liver cancer cell line </td></tr> </tbody> </table>										Community	CCLE_Liver	scHBV	scHCV	TCGA_LIHC	tcHBV	tcHCV	ImmuneSignatures	LiverSignatures	StemSignatures	Community 5	Module 8, Module 55, Module 67, Module 71, Module 72, Module 77, Module 81, Module 92, Module 121, Module 124, Module 145, Module 150	Module 23, Module 29, Module 33, Module 71, Module 81, Module 82	Module 8, Module 24, Module 41, Module 83, Module 83, Module 97	Module 12, Module 22, Module 24, Module 36, Module 42, Module 51, Module 53, Module 63, Module 64, Module 70, Module 75, Module 85, Module 92, Module 110, Module 117, Module 120, Module 128, Module 142	Module 10, Module 45, Module 48, Module 83, Module 97, Module 109, Module 128, Module 129, Module 137, Module 138, Module 139, Module 145	Module 8, Module 57, Module 58, Module 74, Module 79, Module 83, Module 96	HOSHIDA_LIVER_CANCER_LATE_RECURRENCE_DN, HOSHIDA_LIVER_CANCER_SUBCLASS_S3, HOSHIDA_LIVER_CANCER_SURVIVAL_DN	0	 Community 5		<ul style="list-style-type: none"> ➤ Genes from 'subtype S3' signature of hepatocellular carcinoma (HCC): hepatocyte differentiation ➤ Survival signature genes defined in adjacent liver tissue: genes correlated with good survival of hepatocellular carcinoma (HCC) patients ➤ Liver specific genes from Human Gene Expression Index, the HuGE Index, http://www.hugeindex.org ➤ APOC3 pan-etiology driver of HCV and HBV virus-induced HCC validated in all 6 data sources using genetic perturbations of APOC3 in the HepG2 liver cancer cell line 									
Community	CCLE_Liver	scHBV	scHCV	TCGA_LIHC	tcHBV	tcHCV	ImmuneSignatures	LiverSignatures	StemSignatures																																																															
Community 3	Module 4, Module 5, Module 10, Module 12, Module 20, Module 21, Module 27, Module 32, Module 33, Module 41, Module 47, Module 50, Module 57, Module 58, Module 61, Module 85, Module 90, Module 95, Module 98, Module 111, Module 113, Module 117, Module 119, Module 126, Module 127, Module 137, Module 140, Module 142, Module 148	Module 1, Module 2, Module 3, Module 4, Module 5, Module 10, Module 11, Module 12, Module 20, Module 22, Module 25, Module 26, Module 27, Module 28, Module 30, Module 37, Module 39, Module 40, Module 44, Module 48, Module 50, Module 54, Module 55, Module 58, Module 60, Module 62, Module 72, Module 74, Module 80, Module 83, Module 85, Module 93, Module 99, Module 100	Module 2, Module 5, Module 6, Module 10, Module 11, Module 18, Module 25, Module 34, Module 45, Module 48, Module 49, Module 51, Module 52, Module 53, Module 60, Module 61, Module 62, Module 65, Module 67, Module 74, Module 77, Module 79, Module 80, Module 84, Module 86, Module 87, Module 90, Module 92, Module 98, Module 104, Module 111, Module 118, Module 121, Module 125, Module 143, Module 144, Module 149	Module 14, Module 15, Module 30, Module 40, Module 51, Module 65, Module 70, Module 82, Module 92, Module 107, Module 111, Module 118, Module 121, Module 125, Module 143, Module 144, Module 149	Module 6, Module 19, Module 27, Module 52, Module 54, Module 71, Module 82, Module 88, Module 97, Module 99, Module 111, Module 120, Module 129	0	HOSHIDA_LIVER_CANCER_SUBCLASS_S2	BENPORATH_MYC_MAX_TARGETS, BENPORATH_MYC_TARGETS_WITH_EBOX, BENPORATH_NANOG_TARGETS, BENPORATH_OCT4_TARGETS, BENPORATH_SOX2_TARGETS	 Community 3																																																															
<ul style="list-style-type: none"> ➤ Genes from 'subtype S2' signature of hepatocellular carcinoma (HCC): proliferation, MYC and AKT1 activation ➤ MYC targets; targets of c-Myc and Max identified by ChIP on chip in a Burkitt's lymphoma cell line; overlap set; and in cultured cell lines, focusing on E-box-containing genes; high affinity bound subset ➤ CORE stemness genes upregulated and identified by ChIP on chip as NOS (Nanog, OCT4, SOX2) transcription factor targets in human embryonic stem cells ➤ STX7 pan-etiology driver of HCV and HBV virus-induced HCC 																																																																								
<table border="1"> <thead> <tr> <th>Community</th><th>CCLE_Liver</th><th>scHBV</th><th>scHCV</th><th>TCGA_LIHC</th><th>tcHBV</th><th>tcHCV</th><th>ImmuneSignatures</th><th>LiverSignatures</th><th>StemSignatures</th></tr> </thead> <tbody> <tr> <td>Community 5</td><td>Module 8, Module 55, Module 67, Module 71, Module 72, Module 77, Module 81, Module 92, Module 121, Module 124, Module 145, Module 150</td><td>Module 23, Module 29, Module 33, Module 71, Module 81, Module 82</td><td>Module 8, Module 24, Module 41, Module 83, Module 83, Module 97</td><td>Module 12, Module 22, Module 24, Module 36, Module 42, Module 51, Module 53, Module 63, Module 64, Module 70, Module 75, Module 85, Module 92, Module 110, Module 117, Module 120, Module 128, Module 142</td><td>Module 10, Module 45, Module 48, Module 83, Module 97, Module 109, Module 128, Module 129, Module 137, Module 138, Module 139, Module 145</td><td>Module 8, Module 57, Module 58, Module 74, Module 79, Module 83, Module 96</td><td>HOSHIDA_LIVER_CANCER_LATE_RECURRENCE_DN, HOSHIDA_LIVER_CANCER_SUBCLASS_S3, HOSHIDA_LIVER_CANCER_SURVIVAL_DN</td><td>0</td><td colspan="2"> Community 5 </td></tr> <tr> <td colspan="10"> <ul style="list-style-type: none"> ➤ Genes from 'subtype S3' signature of hepatocellular carcinoma (HCC): hepatocyte differentiation ➤ Survival signature genes defined in adjacent liver tissue: genes correlated with good survival of hepatocellular carcinoma (HCC) patients ➤ Liver specific genes from Human Gene Expression Index, the HuGE Index, http://www.hugeindex.org ➤ APOC3 pan-etiology driver of HCV and HBV virus-induced HCC validated in all 6 data sources using genetic perturbations of APOC3 in the HepG2 liver cancer cell line </td></tr> </tbody> </table>										Community	CCLE_Liver	scHBV	scHCV	TCGA_LIHC	tcHBV	tcHCV	ImmuneSignatures	LiverSignatures	StemSignatures	Community 5	Module 8, Module 55, Module 67, Module 71, Module 72, Module 77, Module 81, Module 92, Module 121, Module 124, Module 145, Module 150	Module 23, Module 29, Module 33, Module 71, Module 81, Module 82	Module 8, Module 24, Module 41, Module 83, Module 83, Module 97	Module 12, Module 22, Module 24, Module 36, Module 42, Module 51, Module 53, Module 63, Module 64, Module 70, Module 75, Module 85, Module 92, Module 110, Module 117, Module 120, Module 128, Module 142	Module 10, Module 45, Module 48, Module 83, Module 97, Module 109, Module 128, Module 129, Module 137, Module 138, Module 139, Module 145	Module 8, Module 57, Module 58, Module 74, Module 79, Module 83, Module 96	HOSHIDA_LIVER_CANCER_LATE_RECURRENCE_DN, HOSHIDA_LIVER_CANCER_SUBCLASS_S3, HOSHIDA_LIVER_CANCER_SURVIVAL_DN	0	 Community 5		<ul style="list-style-type: none"> ➤ Genes from 'subtype S3' signature of hepatocellular carcinoma (HCC): hepatocyte differentiation ➤ Survival signature genes defined in adjacent liver tissue: genes correlated with good survival of hepatocellular carcinoma (HCC) patients ➤ Liver specific genes from Human Gene Expression Index, the HuGE Index, http://www.hugeindex.org ➤ APOC3 pan-etiology driver of HCV and HBV virus-induced HCC validated in all 6 data sources using genetic perturbations of APOC3 in the HepG2 liver cancer cell line 																																									
Community	CCLE_Liver	scHBV	scHCV	TCGA_LIHC	tcHBV	tcHCV	ImmuneSignatures	LiverSignatures	StemSignatures																																																															
Community 5	Module 8, Module 55, Module 67, Module 71, Module 72, Module 77, Module 81, Module 92, Module 121, Module 124, Module 145, Module 150	Module 23, Module 29, Module 33, Module 71, Module 81, Module 82	Module 8, Module 24, Module 41, Module 83, Module 83, Module 97	Module 12, Module 22, Module 24, Module 36, Module 42, Module 51, Module 53, Module 63, Module 64, Module 70, Module 75, Module 85, Module 92, Module 110, Module 117, Module 120, Module 128, Module 142	Module 10, Module 45, Module 48, Module 83, Module 97, Module 109, Module 128, Module 129, Module 137, Module 138, Module 139, Module 145	Module 8, Module 57, Module 58, Module 74, Module 79, Module 83, Module 96	HOSHIDA_LIVER_CANCER_LATE_RECURRENCE_DN, HOSHIDA_LIVER_CANCER_SUBCLASS_S3, HOSHIDA_LIVER_CANCER_SURVIVAL_DN	0	 Community 5																																																															
<ul style="list-style-type: none"> ➤ Genes from 'subtype S3' signature of hepatocellular carcinoma (HCC): hepatocyte differentiation ➤ Survival signature genes defined in adjacent liver tissue: genes correlated with good survival of hepatocellular carcinoma (HCC) patients ➤ Liver specific genes from Human Gene Expression Index, the HuGE Index, http://www.hugeindex.org ➤ APOC3 pan-etiology driver of HCV and HBV virus-induced HCC validated in all 6 data sources using genetic perturbations of APOC3 in the HepG2 liver cancer cell line 																																																																								

Community-AMARETTO report: http://portals.broadinstitute.org/pocheplat/demo/cAMARETTO_Liver_6DS/index.html

NDEX network visualization: <http://www.ndexbio.org/#/network/f50b3ecb-7b47-11e9-848d-0ac135e8bacf>

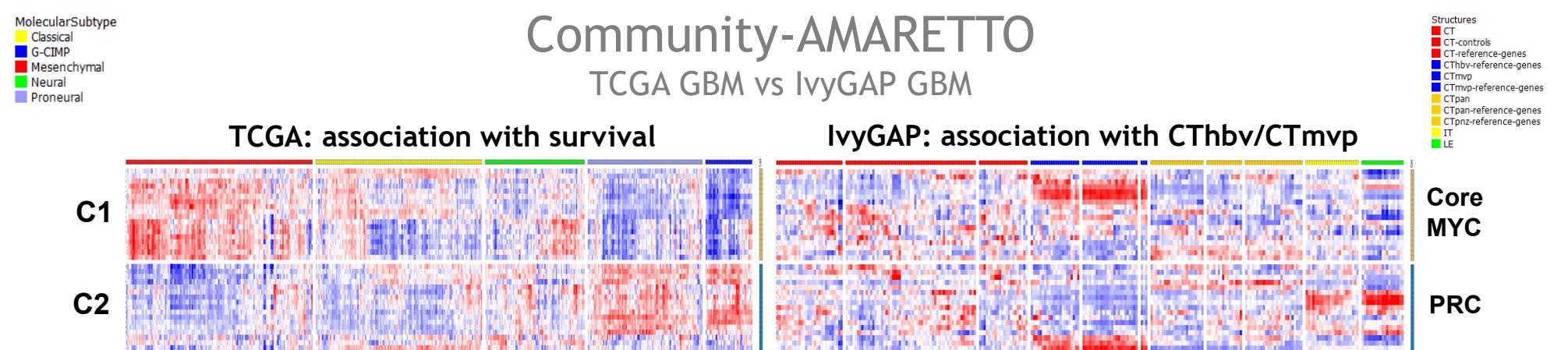
Applications: Multimodal and Multiscale Inference in Cancer

3. Studying multi-omics and imaging of gliomas

Driver prediction for multi-omics subnetworks associated with imaging-derived features representing prognostic molecular subclasses of gliomas and glioblastoma multiforme



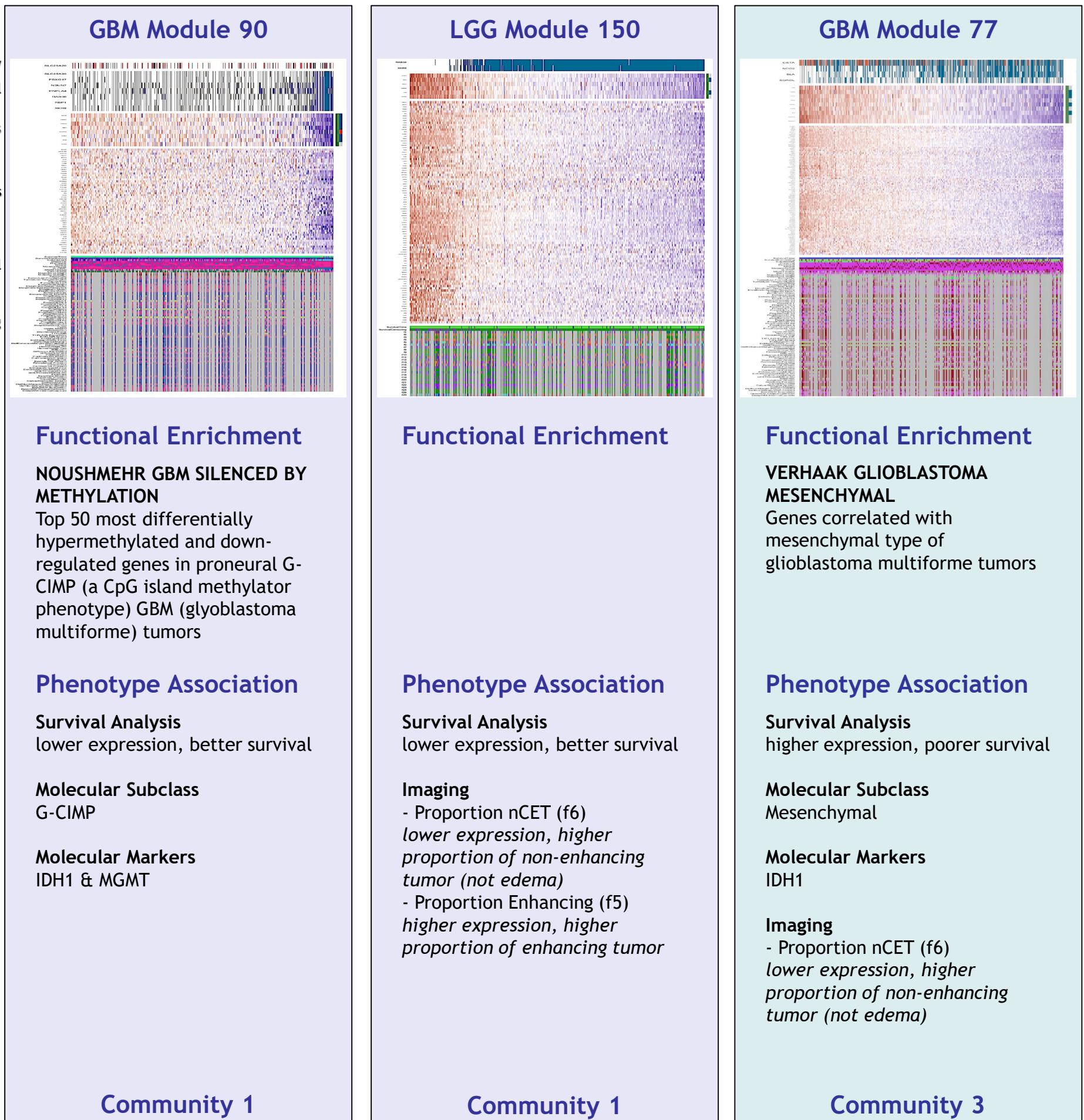
Community	TCGA_GBM	TCGA_LGG	ImmuneSignatures	StemSignatures	
Community 1	Module 3, Module 6, Module 18, Module 22, Module 23, Module 24, Module 25, Module 27, Module 33, Module 37, Module 38, Module 39, Module 41, Module 43, Module 48, Module 54, Module 60, Module 62, Module 66, Module 67, Module 68, Module 71, Module 72, Module 75, Module 78, Module 80, Module 81, Module 82, Module 85, Module 86, Module 87, Module 88, Module 90, Module 91, Module 97, Module 98, Module 99, Module 102, Module 107, Module 110, Module 114, Module 116, Module 117, Module 120, Module 122, Module 129, Module 132, Module 137, Module 138, Module 142, Module 147, Module 150	Module 2, Module 7, Module 8, Module 16, Module 18, Module 19, Module 23, Module 26, Module 27, Module 30, Module 34, Module 35, Module 37, Module 40, Module 43, Module 44, Module 47, Module 50, Module 51, Module 53, Module 55, Module 59, Module 60, Module 61, Module 63, Module 64, Module 66, Module 69, Module 72, Module 79, Module 80, Module 81, Module 83, Module 84, Module 85, Module 86, Module 87, Module 88, Module 89, Module 93, Module 99, Module 102, Module 103, Module 104, Module 110, Module 112, Module 117, Module 120, Module 123, Module 127, Module 133, Module 134, Module 135, Module 137, Module 138, Module 141, Module 142, Module 147, Module 150	CIBERSORT_MAST_CELLS_RESTING	BENPORATH_EED_TARGETS, BENPORATH_ES_WITH_H3K27ME3, BENPORATH_NOS_TARGETS, BENPORATH_OCT4_TARGETS, BENPORATH_PRC2_TARGETS, BENPORATH_SUZ12_TARGETS	
	➤ VERHAAK GLIOBLASTOMA PRONEURAL: Genes correlated with proneural type of glioblastoma multiforme tumors ➤ NOUSHMEHR GBM SILENCED BY METHYLATION: Top 50 most differentially hypermethylated and down-regulated genes in proneural G-CIMP (a CpG island methylator phenotype) GBM (glioblastoma multiforme) tumors ➤ Molecular markers: PDGFRA, IDH1 and MGMT ➤ Methylation-driven drivers shared between GBM (Module 90) and LGG (Module 77): FBXO17, XKR8, RAB34/36 ➤ Survival analysis: hypermethylated drivers, repressed expression of drivers and targets, and association with better survival rates in the G-CIMP and proneural molecular subclasses				Community 1
Community 3	Module 8, Module 55, Module 70, Module 77, Module 93, Module 125, Module 131, Module 133, Module 134, Module 141	Module 22, Module 33, Module 38, Module 73, Module 90, Module 118, Module 121	CIBERSORT_EOSINOPHILS, CIBERSORT_MACROPHAGES_M0, CIBERSORT_MACROPHAGES_M2, CIBERSORT_MONOCYTES, CIBERSORT_NEUTROPHILS	0	
	➤ VERHAAK GLIOBLASTOMA MESENCHYMAL: Genes correlated with mesenchymal type of glioblastoma multiforme tumors ➤ Enriched for immune cell type-specific signatures ➤ Associated with imaging feature Proportion nCET (f6): lower expression, higher proportion of non-enhancing tumor (not edema) ➤ Survival analysis: induced expression of drivers and targets and association with poorer survival rates in the mesenchymal molecular subclass				Community 3



Community-AMARETTO report: http://portals.broadinstitute.org/pocheplat/demo/cAMARETTO_Brain_2DS/index.html
 NDEX network visualization: <http://www.ndexbio.org/#/network/c1f0fccf-80b6-11e9-848d-0ac135e8bacf>

Applications: Multimodal and Multiscale Inference in Cancer

3. Studying multi-omics and imaging of gliomas



*AMARETTO tools and resources

Software availability: *AMARETTO is available via GitHub, Bioconductor, Jupyter Notebook, GenePattern, GenomeSpace, GenePattern Notebook.



References, Tools and Resources:

<http://portals.broadinstitute.org/pochetlab/amaretto.html>

Funding: NIH NCI ITCR R21 CA209940 (Pochet), NIH NIAID R03 AI131066 (Pochet), NIH NCI ITCR U01 CA214846 collaborative suppl. (Carey/Pochet)