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Ministero dell'Università e della Ricerca

Italiadomani
PIANO NAZIONALE DI RIPRESA E RESILIENZA

ICSC
Centro Nazionale di Ricerca in HPC, Big Data and Quantum Computing

ICSC

Centro Nazionale di Ricerca in HPC,
Big Data and Quantum Computing

ANNUAL MEETING

Del Centro Nazionale di Ricerca in HPC, BIG DATA AND QUANTUM COMPUTING

ISOLA D'ELBA – LA BIODOLA, 5 - 8 OTTOBRE 2025

Spoke 8 - In Silico Medicine WPs

WP1 - Implementation of modelling & simulation platforms (open Source and commercial) through HPC solvers

- identifying methodologies for implementing HPC solvers within the project
- developing In Silico model platforms through the use of identified HPC solvers, and handling the optimization and scalability of these models

WP2 - Digital twins and in silico trials

- development of vertical solutions for In Silico Trials
- development of vertical solutions for Digital Twins in healthcare
- definition of specifications and prototypes for a Virtual Human Twin infrastructure

WP3 - Integrated digital data flow between clinics and HPC centers and Easy-to-use GUI for HPC solvers (hiding complexity for ultimate users)

- data exchange between healthcare facilities, such as hospitals and clinics, and HPC centers
- monitoring the adoption at national level of the law on data governance
- the implementation of the infrastructure that manages the flow of final clinical data, and the development of a web-based user interface

WP1–WP2: Solvers, In Silico Trials & Digital Twins

• **HPC & Solver Optimization (WP1)**:

WP1 focused on adapting and optimizing simulation tools for high-performance computing (HPC) to enable large-scale biomedical modeling.

Several solvers — from molecular dynamics (GROMACS, AMBER) to AI frameworks (TensorFlow, PyTorch) and brain simulators (TVB, BSB) — were profiled and optimized on CINECA's Leonardo and ADAcloud infrastructures.

• **In Silico Trials (IST) & Digital Twins (DTH) (WP2)** :

Over the past three years, WP2 has consolidated a suite of In Silico Medicine solutions that bridge advanced computation and clinical translation.

Seven In Silico Trial platforms (e.g., UISS-COVID19, BoneStrength, IST4JR) and eight Digital Twins (e.g., UISS-MS-MRI, PHENSIM, BBCT-Hip, PlasticBrain) were developed and validated across European HPC and cloud infrastructures.

These tools address diverse biomedical challenges — from immune response simulation and vaccine design to fracture risk prediction and neuro-musculoskeletal modeling — showcasing the power of HPC to accelerate discovery and decision support.

WP3: Cost, Scalability & Impact

WP3 focused on bridging the gap between advanced computational models and clinical usability, ensuring that Digital Twin technologies can be realistically adopted in healthcare settings.

The work centered on two flagship solutions — BBCT-Hip (orthopaedic risk prediction) and UISS-MS-MRI (multiple sclerosis management) — to evaluate their ease of use, computational requirements, and economic sustainability when deployed on the ICSC/INFN EPIC Cloud infrastructure.

A major achievement was demonstrating that highly sophisticated in silico tools can be used intuitively by clinicians through user-friendly interfaces, hiding the underlying HPC and AI complexity.

Both applications were assessed for cost-effectiveness, confirming their economic viability under AIFA thresholds.

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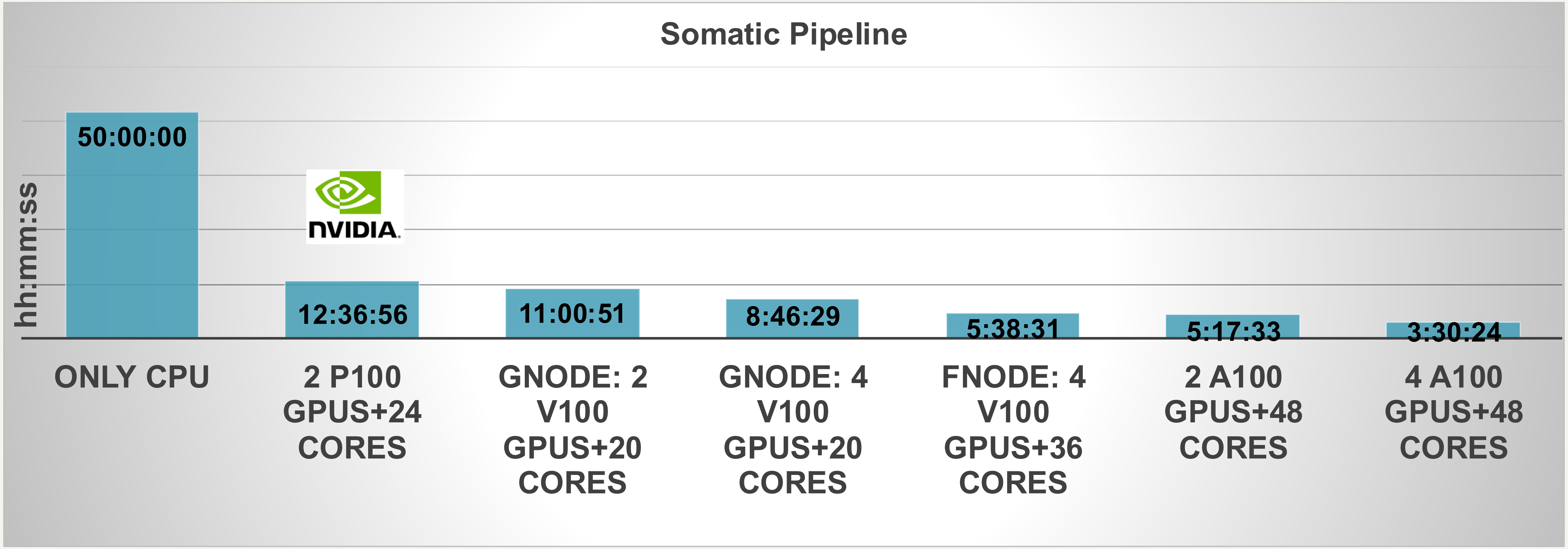
ICSC Centro Nazionale di Ricerca in HPC, Big Data and Quantum Computing

Genetics and Genomics of Pancreatic Ductal Adenocarcinoma (PDAC)

Andrea Cavalli

Genomics & HPC



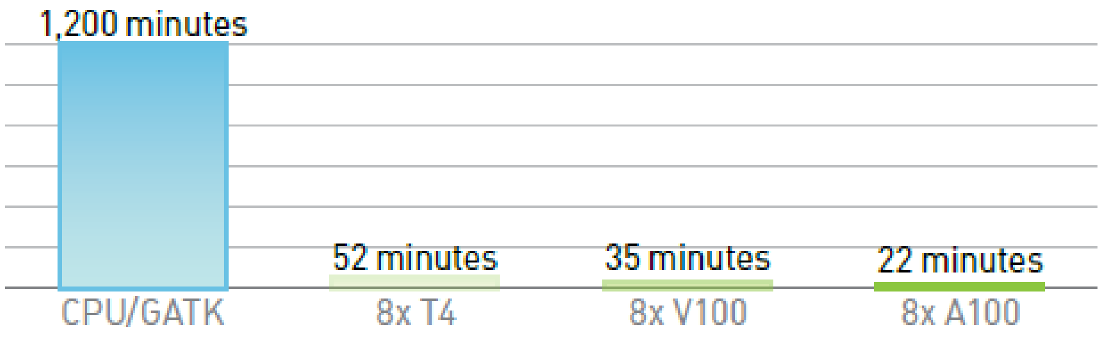
Using a FAT node (with 4 V100 GPUs, 36 cores) leads up to 1.6x speed up than using a GPU node (with 4 V100 GPUs, 20 Cores)

Using 8 A100 GPUs and 128 cores leads up to just 1.1x speed up than using 4 A100 GPUs and 128 cores

Parabricks performance over different GPUs generation and number: some references

PERFORMANCE COMPARISON

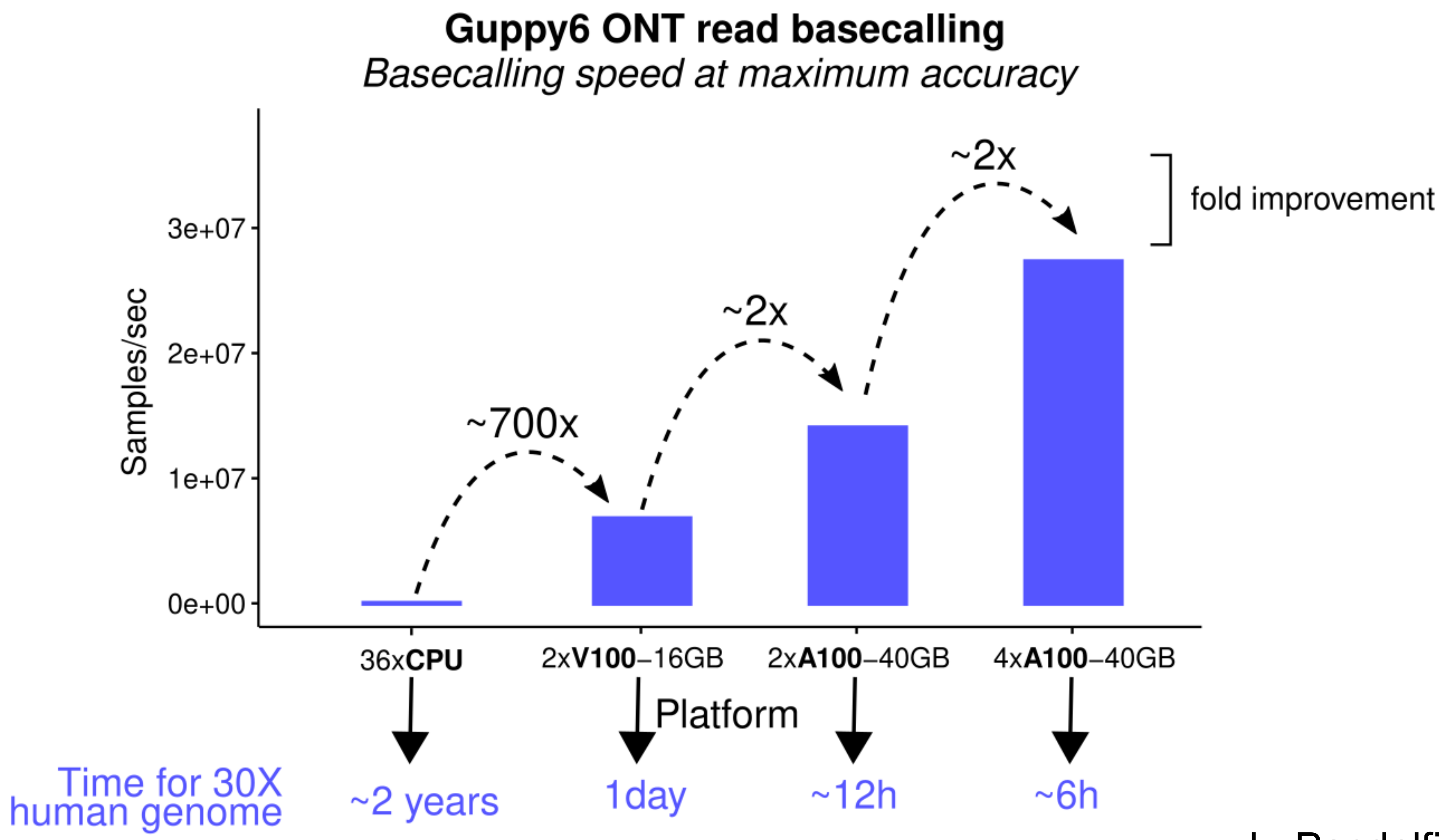
Germline End-to-End Secondary Analysis



Data was generated using publicly available data (https://precision.fda.gov/challenges/truth) for NA12878, deprecating the data to 30X coverage. For the 22-minute runtime, DGX A100 with 320G memory was used. The native GATK4.1 numbers were generated using 32 vCPU (3.1 GHz Intel Xeon® Platinum 8175M) using 28Gb RAM.

https://www.nvidia.com/en-us/clara/genomics/

PromeTHION (Nanopore) – Long reads



L. Pandolfini

TITOLO SEZIONE

@Andrea: Proof of concept PDAC genomics in Humanitas and Infermi Hospital Rimini

Clinical genomics with direct impact on patients

Research activities for novel discoveries in PDAC

Pancreatic Cancer Cohorts

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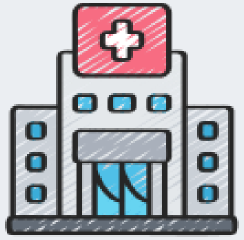
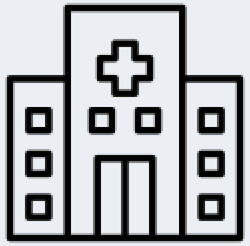


Humanitas Research Hospital
Milan

VICTORIA Study Protocol
Visceral cancer

- ❑ Prospectively recruited ~180 Pts PDAC (→ PDOs)
- ❑ Retrospective biobanked 58 Pts PDAC
- ❑ Retrospective biobanked 46 Pts Ampullary Cancer

SERVIZIO SANITARIO REGIONALE EMILIA-ROMAGNA



Infermi Hospital
Rimini

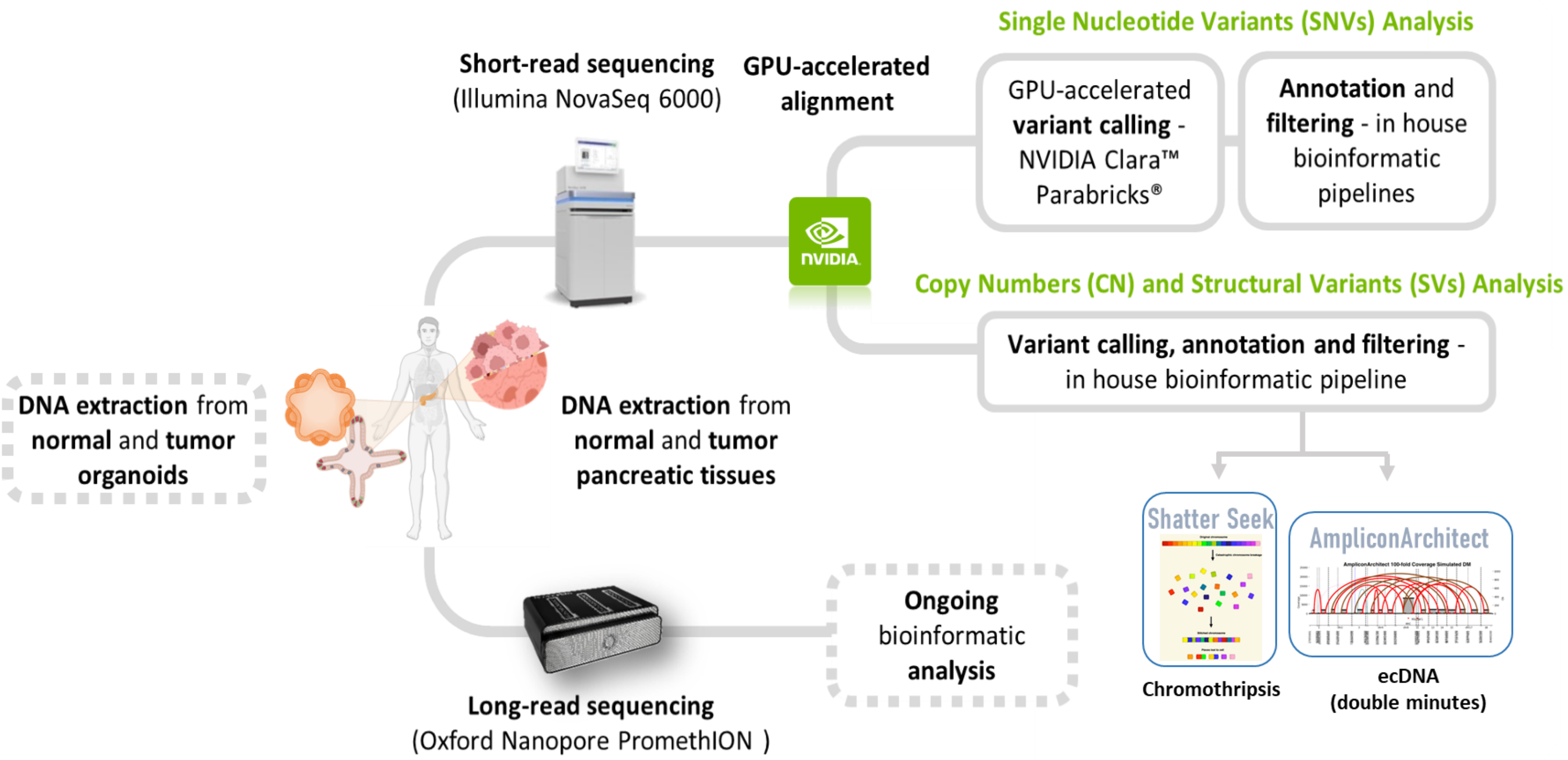
PILOT WGS Study Protocol
Pancreatic cancer

- ❑ Prospectively recruited 56 Pts PDAC

Genomes of Pts sequenced N=452

Combined study cohort N=340

Schematic Overview of the Experimental Workflow



Marangoni S., Furia F.* Vecchi M.#, Landuzzi F. # Cavalli A# et al. 2025 Submitted*

Germline Analysis of SNVs in the two Italian PDAC Cohorts

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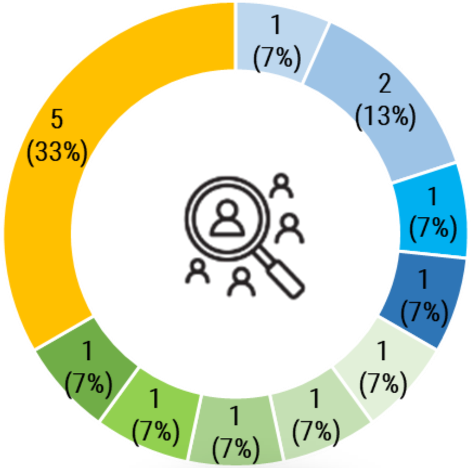
Retrospective Cohort
$N_{pts} = 55$



Key facts

BRCA2, *ATM*, *CHEK2*, *MLH1*	~ 9% (N=5) → germline P/LP variants in genes predisposing to PDAC
MSR1, *RNASEL*, *LZTR1*, *CTNND1*, *USP8*	~ 9% (N=5) → germline P/LP variants in genes predisposing to other cancers
CFTR	~ 9% (N=5) → germline P/LP variants in genes of chronic pancreatitis-associated syndromes

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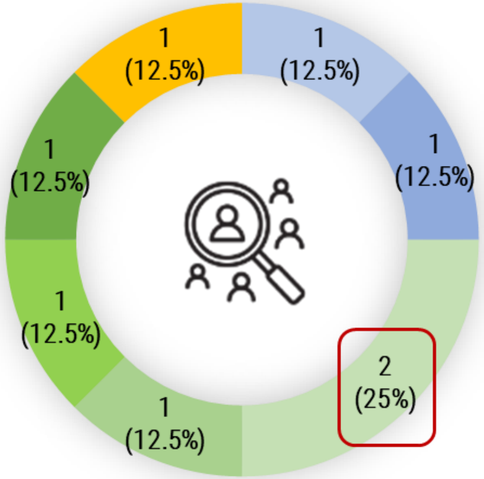
Interim analysis Prospective Cohort
$N_{pts} = 39$



BRCA2, *ATM*	~ 5% (N=2) → germline P/LP variants in genes predisposing to PDAC
RAD51C, *PRF1*, *MLP*, *JAK2*	~ 13% (N=4) → germline P/LP variants in genes predisposing to other cancers
CFTR	~ 2.6% (N=1) → germline P/LP variants in genes of chronic pancreatitis-associated syndromes

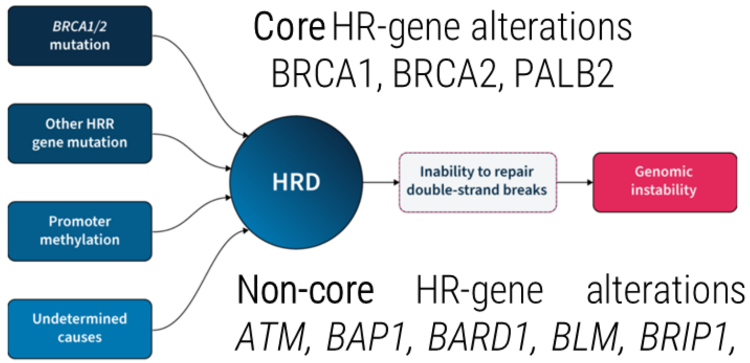
RAD51C: a New PDAC Cancer Susceptibility Gene

J Gastrointest Oncol. 2018 Aug;9(4):E19–E22. doi: 10.21037/jgo.2018.03.11

Exceptional response to FOLFIRINOX in a patient with pancreatic cancer and a germline *RAD51C* mutation

Sofia Palacio [1], Terri Pollack [1], Rachel Silva-Smith [1], Daniel A Sussman [1], Peter J Hosein [1,✉]

- ❑ Predictive biomarker of therapy response → potential benefit from platinum-based chemotherapy;
- ❑ *RAD51C* status as a biomarker for patient stratification and clinical trial eligibility (maintenance olaparib, pembrolizumab + olaparib, others)



Core HR-gene alterations
BRCA1, BRCA2, PALB2

Non-core HR-gene alterations
ATM, BAP1, BARD1, BLM, BRIP1, CHEK2, FAM175A, FANCA, FANCC, NBN, RAD50, RAD51, RAD51C, RTEL1

Germline gene testing: implementation of the ESMO gene panel in our cohorts

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

SPECIAL ARTICLE

Germline-focused analysis of tumour-detected variants in 49,264 cancer patients: ESMO Precision Medicine Working Group recommendations

Z. Kuzbari[1†], C. Bandlamudi[2†], C. Loveday[1], A. Garrett[1], M. Mehine[2], A. George[1,3], H. Hanson[1,4], K. Snape[4], A. Kulkarni[5], S. Allen[1], S. Jezdic[6], R. Ferrandino[6], C. B. Westphalen[7], E. Castro[8], J. Rodon[9], J. Mateo[10,11], G. J. Burghel[12], M. F. Berger[2],

Box 1. Recommendations for genes for inclusion for germline-focused analysis and follow-up

CSG actionability class	All ages			Age <30
Most	BRCA1 BRCA2	MLH1 MSH2	MSH6 PALB2 RET	
High	BRIP1 MUTYH[c] PMS2 RAD51C	RAD51D SDHAF2[d] SDHB SDHC[d]	SDHD[d] TMEM127[d] **TSC2**[f] VHL[a]	APC **PTEN**[d,f] RB1 **TP53**[b,f]
Standard	ATM **BAP1**[f] BARD1 CHEK2 DICER1	FH FLCN **NF1**[f] PTCH1[e] POLD1	POLE SDHA SMAD3[e] **SMARCB1**[e,f] SUFU[e]	CDKN2A SMARCA4

Germline Actionable Variants in PDAC Patients - OncoKB

SUBJECTS	ACTIONABLE VARIANT	TREATMENTS	ONCOKB LEVEL	CANCER TYPES
2	*BRCA2 Oncogenic mutations*	*Rucaparib*	*2*	Pancreatic Adenocarcinoma, Acinar Cell Carcinoma of the Pancreas
		Olaparib	*3*	Pancreatic Adenocarcinoma, Acinar Cell Carcinoma of the Pancreas
3	*ATM Oncogenic mutations*	*Olaparib Talazoparib+Enzalutamide*	*1*	Prostate cancer
1	*CHEK2 Oncogenic mutations*	*Olaparib Talazoparib+Enzalutamide*	*1*	Prostate Cancer
2	*RAD51C*	*Olaparib Talazoparib+Enzalutamide*	*1*	Prostate Cancer
1	*MLH1 Oncogenic mutations* warrants further investigation	*Talazoparib+Enzalutamide*	*1*	Prostate Cancer

- ❑ Evidence of clinical actionability in ~10% of cases (9/94): HRC-PDC (N=55) + Rimini-PDC (N=39)

Germline Actionable Variants in PDAC Patients - OncoKB

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Cohort HRC (55) + Rimini (39)
N=94 cases

Evidence of clinical actionability in ~10% of cases (9/94)

SUBJECTS	ACTIONABLE VARIANT	TREATMENTS	ONCOKB LEVEL	CANCER TYPES
2	*BRCA2 Oncogenic mutations*	*Rucaparib*	*2*	Pancreatic Adenocarcinoma, Acinar Cell Carcinoma of the Pancreas
		Olaparib	*3*	Pancreatic Adenocarcinoma, Acinar Cell Carcinoma of the Pancreas
3	*ATM Oncogenic mutations*	*Olaparib Talazoparib+Enzalutamide*	*1*	Prostate cancer
1	*CHEK2 Oncogenic mutations*	*Olaparib Talazoparib+Enzalutamide*	*1*	Prostate Cancer
2	*RAD51C*	*Olaparib Talazoparib+Enzalutamide*	*1*	Prostate Cancer
1	*MLH1 Oncogenic mutations* warrants further investigation	*Talazoparib+Enzalutamide*	*1*	Prostate Cancer

- ❑ In ~ 7.4% (7/94): germline P/LP variants predisposing to PDAC (i.e., *BRCA1/2*, *ATM*, *MLH1*, *CHEK2*, etc.)
- ❑ In ~ 9.6% (9/94): germline P/LP variants predisposing to other types of cancers (i.e., *LZTR1*, *RAD51C*, etc.)
- ❑ In ~ 2.1% (2/94): germline P/LP variants in *RAD51C a* non-core HR-gene
  - Biomarker Predictive of therapy response to platinum-based chemotherapy
  - Biomarker for patient stratification in clinical trials (maintenance olaparib, pembrolizumab + olaparib, others)
  - → *RAD51C* a cancer susceptibility gene also in PDAC (?)

Somatic Analysis of SNVs in the HRC-PDAC Cohort (N=52)

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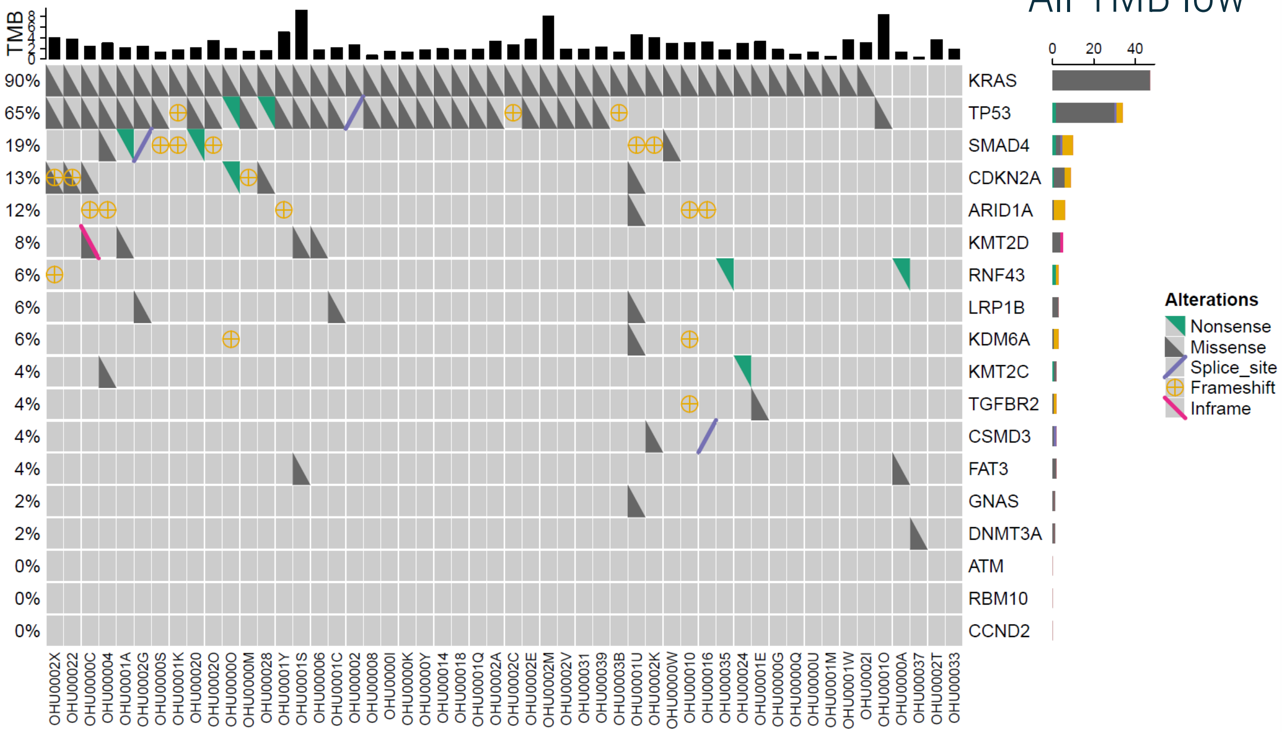
Mutational landscape with Strelka2

All MSS
All TMB low



Credit to Fabio Marchianò and Charlotte Ng

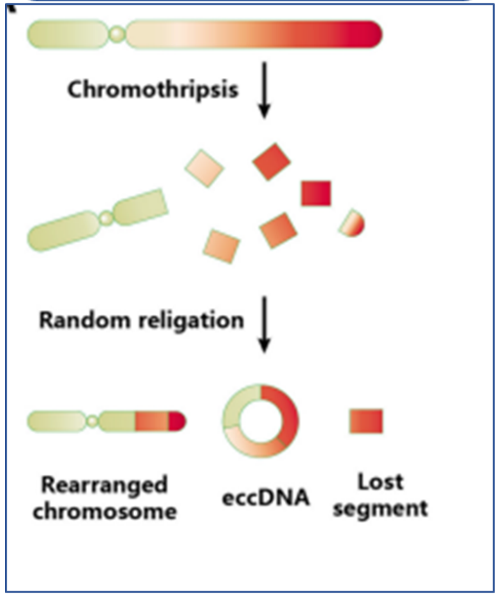
Comparison of mutation frequencies identified in key driver genes reported in TCGA and Korean PDAC cohorts

	HRC cohort (N=52) %	TCGA (N=150) %	Korean Cohort (N=87) %
KRAS	90.0	90.7	94.3
TP53	65.0	69.3	74.7
SMAD4	19.0	24.7	29.9
CDKN2A	13.0	14.7	23.0
GNAS	2.0	6.7	6.9
RNF43	6.0	6.0	10.3
ARID1A	12.0	5.3	11.5
TGFBR2	4.0	5.3	4.6
ATM	0.0	3.3	10.3
DNMT3A	2.0	3.3	1.1

(Adapted from Jung K. et al. 2022 Scientific Reports 12:20937)

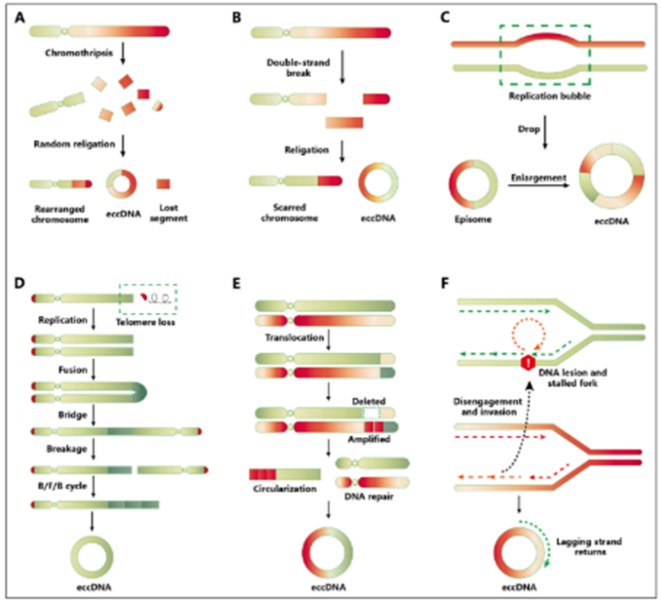
Somatic Analysis of Complex SVs in the HRC-PDAC Retrospective Cohort

Chromothripsis causes DNA fragmentation and a portion of these fragments can be reassembled into ecDNA

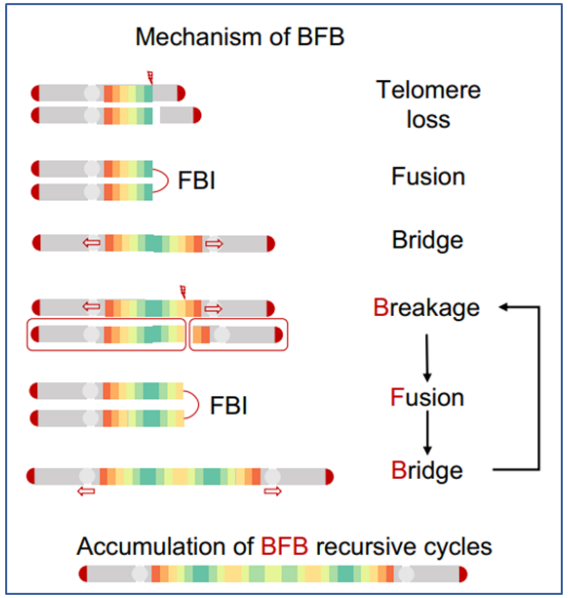


Extrachromosomal circular DNA (eccDNA) originate from chromosomes

→ size range: <100bp-megabases



Breakage-fusion-bridge (BFB) is a complex rearrangement and repetition of BFB cycles contributes to copy number (CN) amplifications

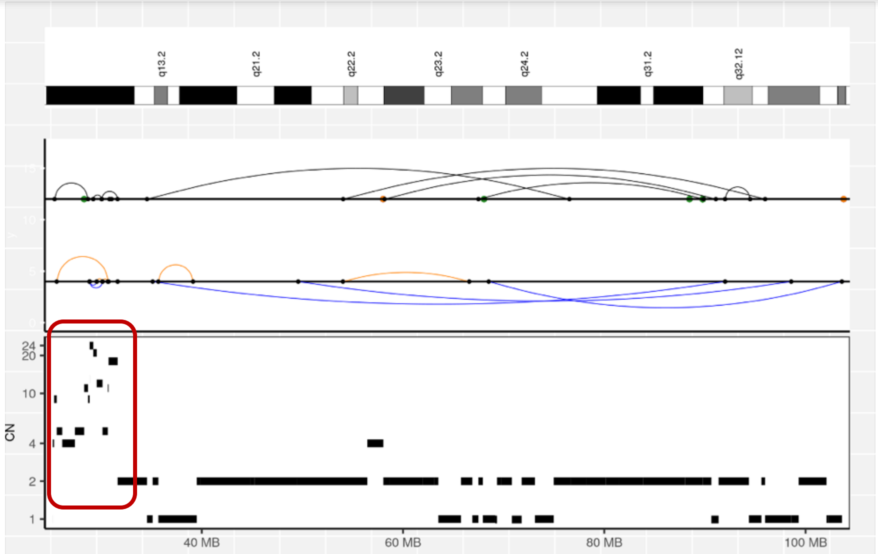


The acentric structure of ecDNA facilitates random segregation, highly elevated CN, intratumoral genetic heterogeneity and rapid tumor evolution → Aggressive tumor growth
→ Therapeutic resistance

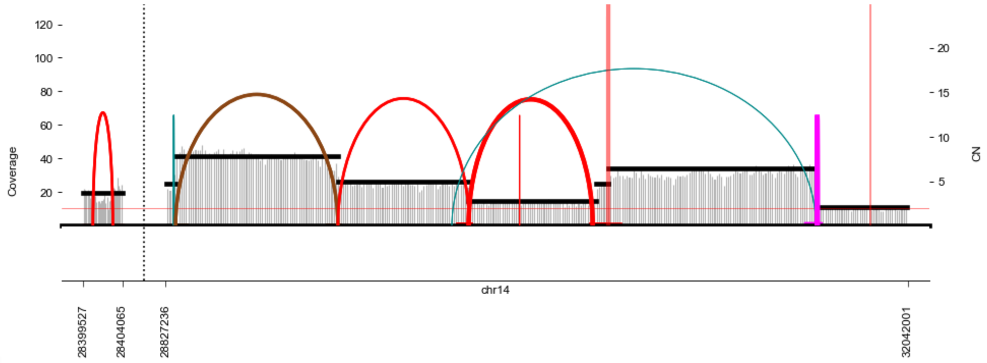
Prevalence of Chromothripsis and ecDNA/BFB events in the HRC-PDAC Cohort (N=52)

Chromothripsis
High confidence chromothripsis events: ~ **33%** (17/52)

ecDNA/BFB
ecDNA+: ~ **6%** (3/52)
BFB+: ~ **8%** (4/52)
ecDNA+ and BFB+: ~ **2%** (1/52)



Chromothripsis event on chromosome 14
PDAC-28



ecDNA+ on chromosome 14
PDAC-28

Analysis of lncRNAs Involved in Complex Genomic Alterations in the HRC-PDAC Cohort

Mapping lncRNAs into focal amplified regions identified by AmpliconArchitect Suite (ecDNA/BFB/CNC/Linear)

LncTarD 2.0

8.360 lncRNAs

- ❑ lncRNAs with an **effect** on the **expression** of the **target**
- ❑ lncRNAs **activity** must be **related to cancer**
- ❑ lncRNA **coordinates** available on **GENCODE**

501 genes encoding for lncRNAs

Amplicon Suite

Map the coordinates of these genes inside the focal amplified regions

Five Pts with lncRNA-encoding genes located wthin focal amplified regions (ecDNA/BFB/CNC/Linear)

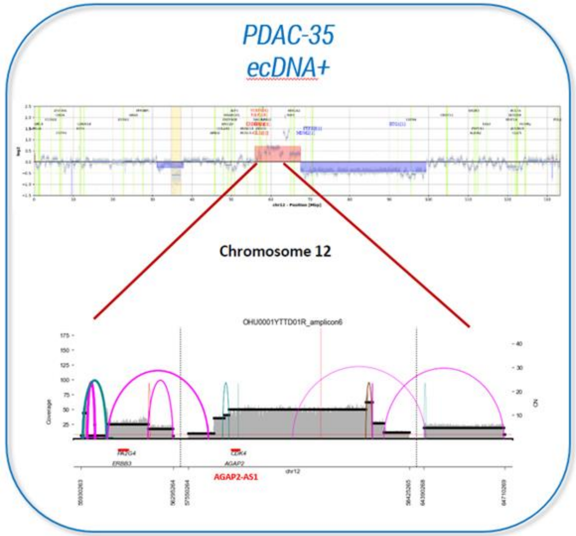
Sample ID	Classification	Chromosome	Amplicon	lncRNA-encoding gene
PDAC-35	ecDNA	12	amplicon6	*AGAP2-AS1, GIHCG*
	BFB	6	amplicon1	*MDC1-AS1*
	BFB	6	amplicon4	*FOXP4-AS1*
PDAC-51	ecDNA	11	amplicon3	*ENSG00000261347*
PDAC-40	BFB	12	amplicon1	*AGAP2-AS1, GIHCG*
PDAC-45	Linear	6	amplicon1	*FOXP4-AS1*
PDAC-57	Linear	8	amplicon2	*LINC00536*
	CNC	8	amplicon1	*PCAT1, CASC19, CCAT2, CASC11, PVT1, CCDC26*

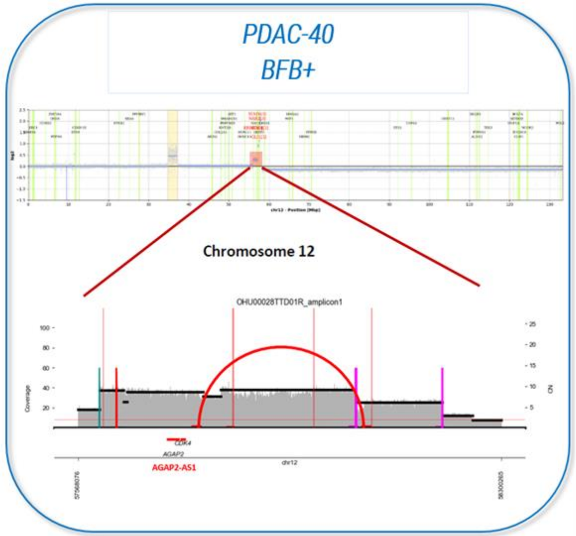
Analysis of lncRNAs Involved in Complex Genomic Alterations in the HRC-PDAC Cohort

Mapping lncRNAs into ecDNA/BFB

Sample ID	AmpliconClassifier	Amplicon	lncRNA-encoding gene	Chromosome	Position start	Position end	Amplicon size
PDAC-35	ecDNA	amplicon6	*AGAP2-AS1 , GIHCG*	12	57687443	58280425	593 kb
	BFB	amplicon1	*MDC1-AS1*	6	30217501	31027098	810 kb
	BFB	amplicon4	*FOXP4-AS1*	6	41546787	42042554	496 kb
PDAC-51	ecDNA	amplicon3	*ENSG00000261347*	11	69464210	69796351	332 kb
PDAC-40	BFB	amplicon1	*AGAP2-AS1 , GIHCG*	12	57605055	58049325	444 kb

AGAP2-AS1





RNASeq analysis

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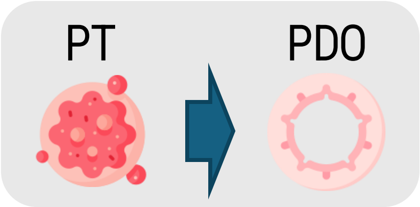
Genomic Characterization of Patient Derived Organoids (PDOs, N=8)

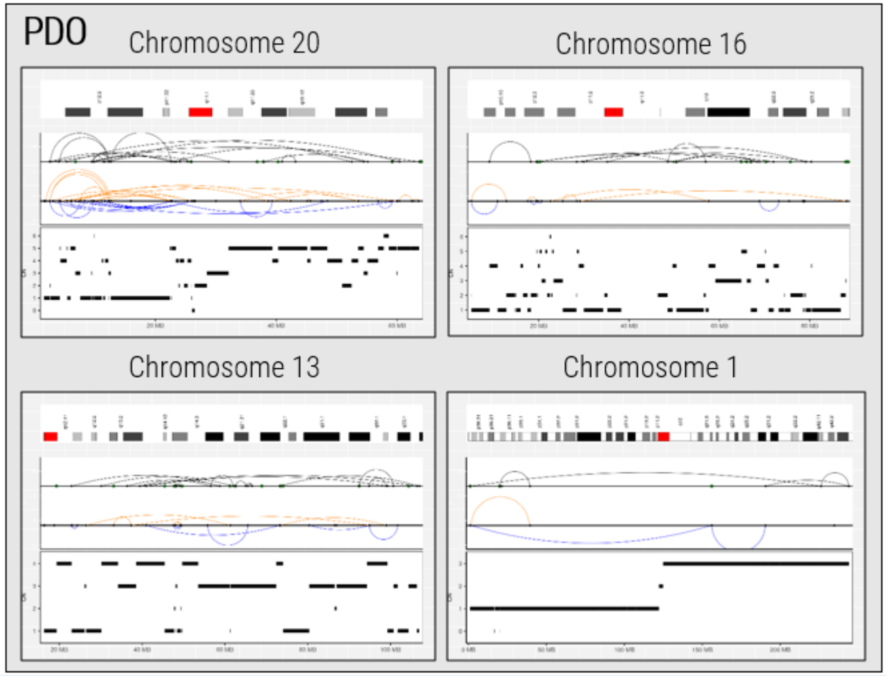


Carola Morell and Salvatore Piscuoglio

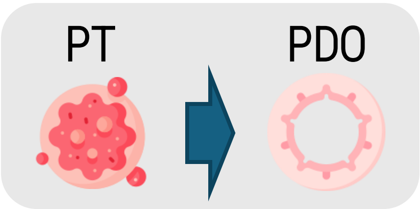
Pt ID	Tissue type	Coverage (WGS)	Facets Ploidy	Facets Purity	*KRAS* (p.Gly12Asp) AF	*TP53* (p.Glu286Gln) AF	*KMT2D* (p.Gln3454*) AF
P033	Primary Tumor	83	2.00	NA	20.00%	31.70%	23.50%
	Tumor Organoid	75	1.92	0.94	49.00%	homozygous	51.20%

chromothripsis

PDO chromothripsis



Genomic Characterization of Patient Derived Organoids (PDOs, N=8)



Carola Morell and Salvatore Piscuoglio

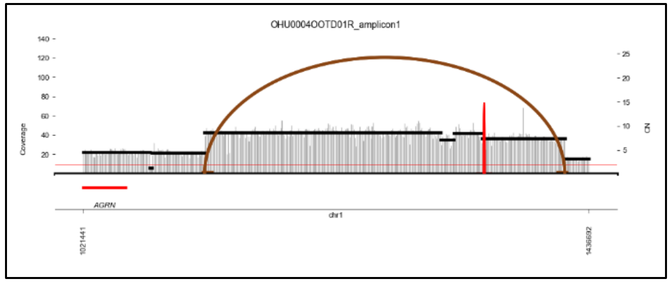
Pt ID	Tissue type	Coverage (WGS)	Facets Ploidy	Facets Purity	*KRAS* (p.Gly12Asp) AF	*TP53* (p.Arg273Cys) AF	*KMT2C* (p.Asp348Asn) AF
P065	Primary Tumor	90	2.10	0.30	4.50%	4.40%	/
	Tumor Organoid	103	1.92	0.96	44.60%	homozygous	4.20%

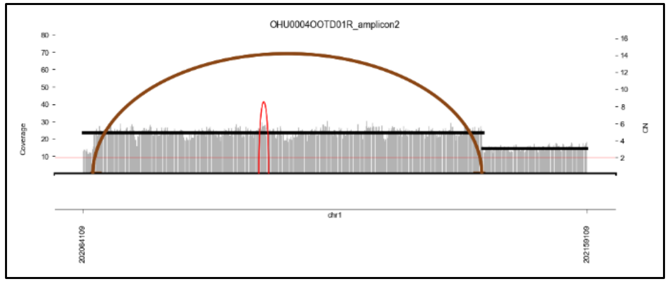
→ ecDNA+

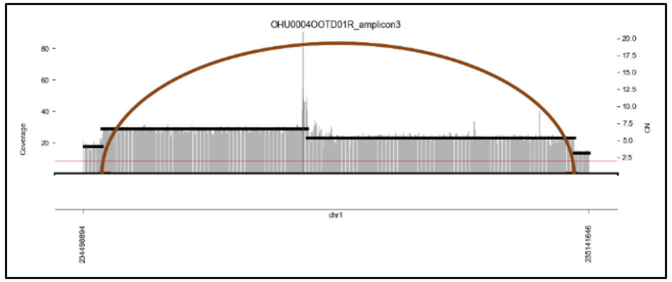
3 different ecDNA+ in chromosome 1

sample_name	amplicon_number	amplicon_decomposition_class	ecDNA+
OHU0004OOTD01R	amplicon1	Cyclic	Positive
OHU0004OOTD01R	amplicon2	Cyclic	Positive
OHU0004OOTD01R	amplicon3	Cyclic	Positive

lncRNAs mapping in these amplicons
LINC01342
LINC01354
LINC00184







scRNASeq analysis on these two organoids in ongoing

Whole Genome Sequencing: A Game-Changer in PDAC Research and Healthcare

Recommendation for genetic testing for all pancreatic cancer patients regardless of their family history (The National Comprehensive Cancer Network - NCCN)

WGS provides enough data to personalize therapeutic approaches and treatments to PDAC (and cancer at large) → select a treatment that will provide the most benefit with the least risk of side effects (best treatment is the treatment that's right for you)

WGS enables the analysis of **lnc-RNAs** and **transposable elements** to identify other types of clinically relevant variation and interpret the impact of many **intronic** and **non-coding** variants in PDAC (and cancer at large)

Whole Genome Sequencing: A Game-Changer in PDAC Research and Healthcare

Recommendation for genetic testing for all pancreatic cancer patients regardless of their family history (The National Comprehensive Cancer Network - NCCN)

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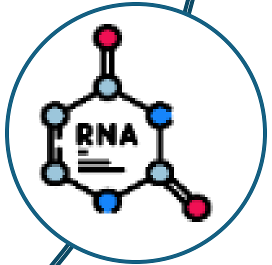
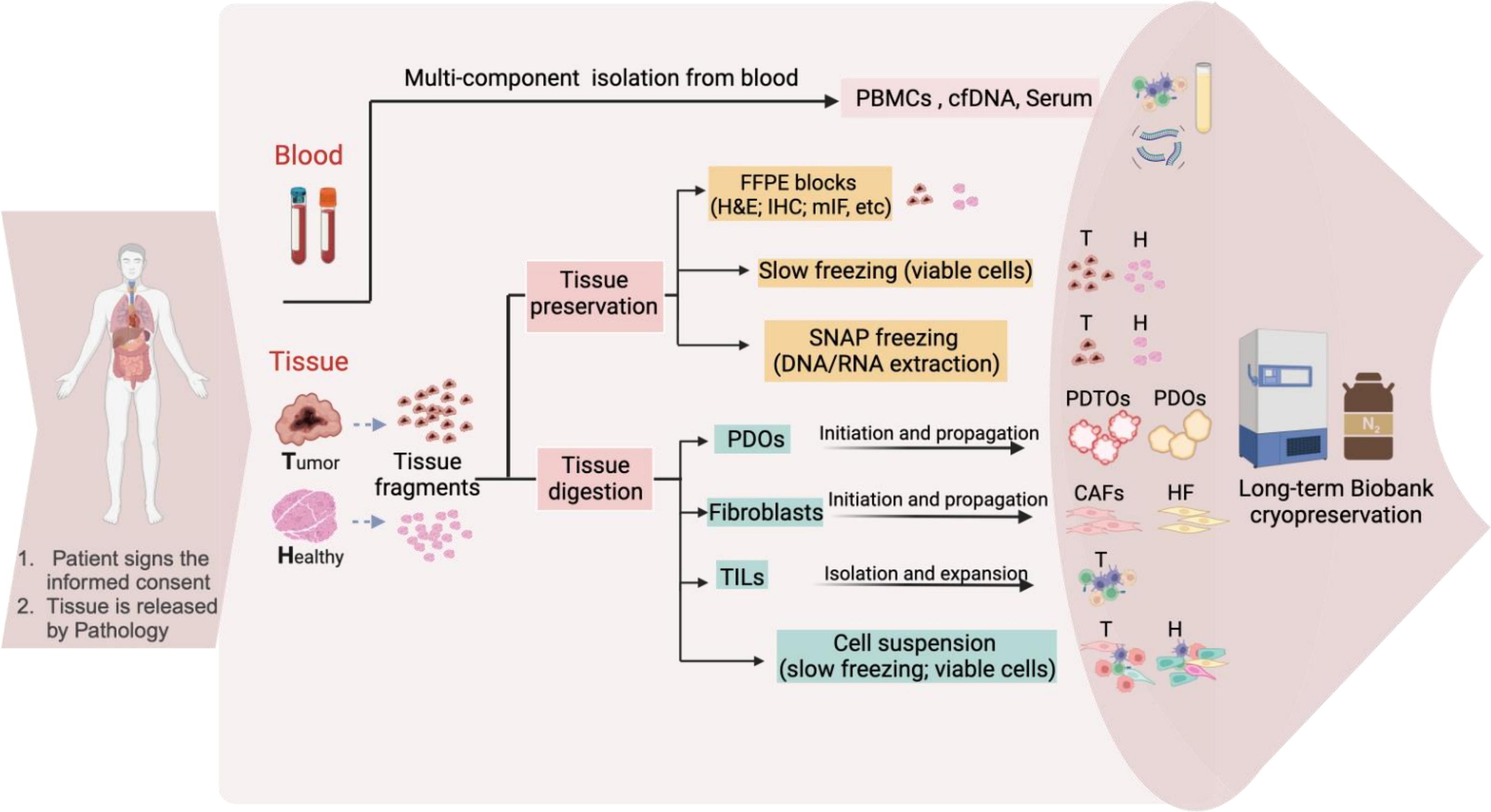
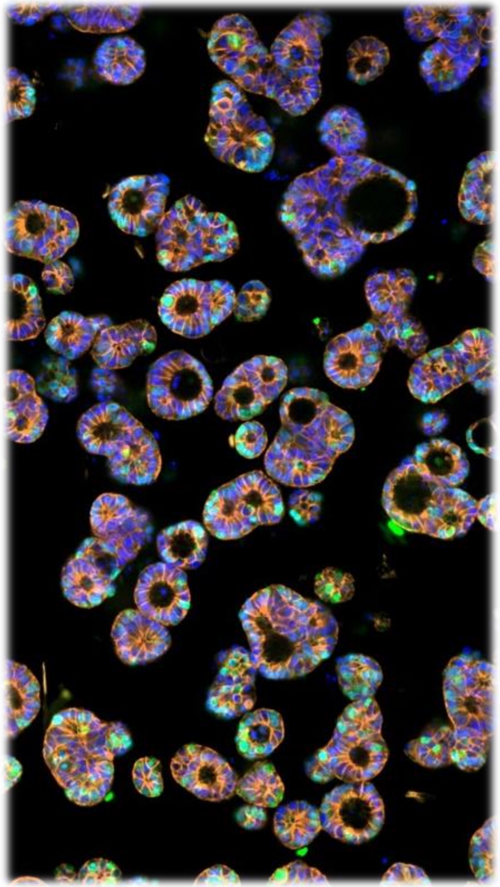


WGS enables the analysis of **lnc-RNAs** and **transposable elements** to identify other types of clinically relevant variation and interpret the impact of many **intronic** and **non-coding** variants in PDAC (and cancer at large)

Establishing a Nationwide Living Biobank

IRCCS HUMANITAS RESEARCH HOSPITAL





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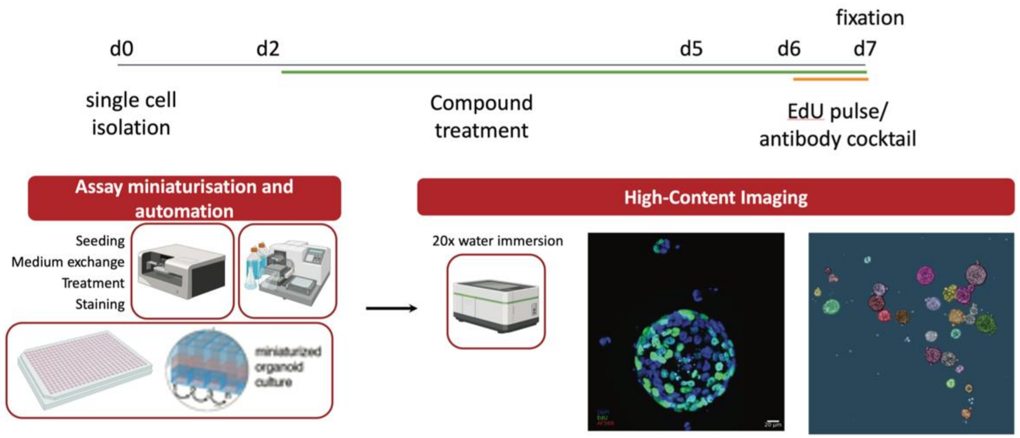
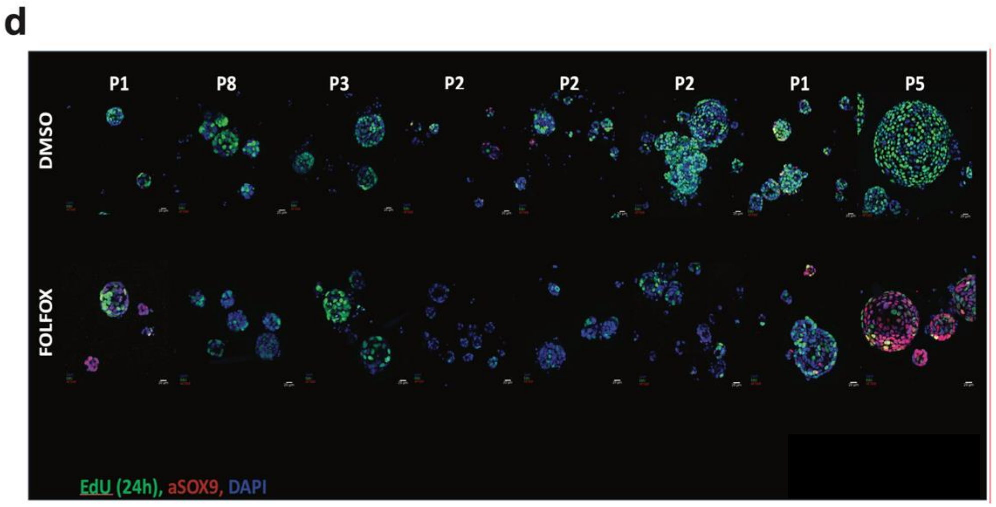
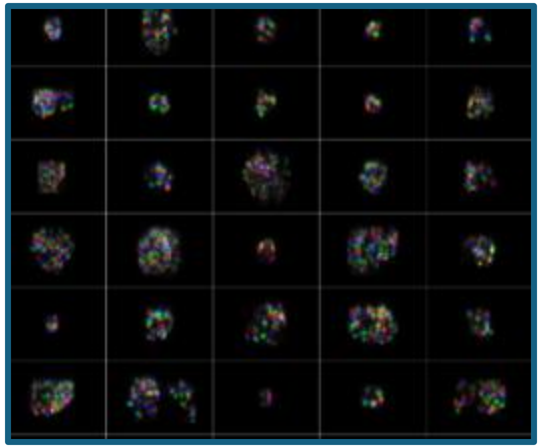
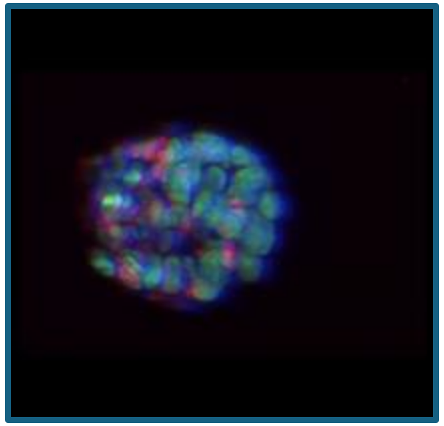
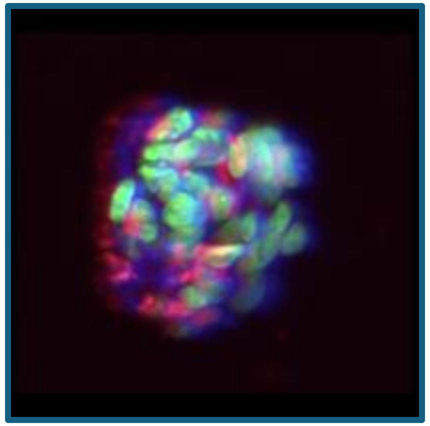
Drug screening and personalized immunotherapy



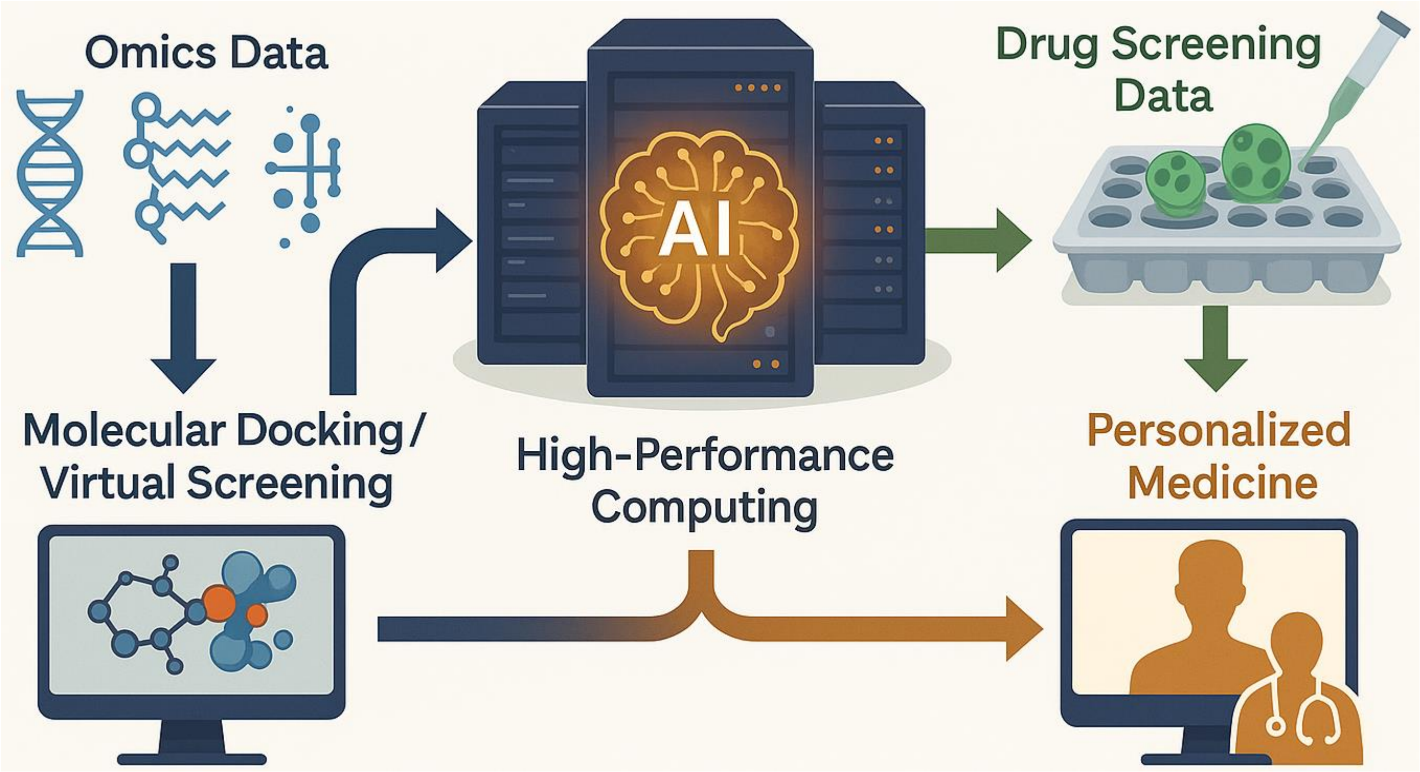








HPC-Driven Personalized Drug Discovery



- **Ricerca oncologica avanzata:** integrazione di dati multi-omici, organoidi e AI per comprendere i meccanismi tumorali e predire la risposta ai trattamenti.
- **Accelerazione della drug discovery:** uso di HPC e screening virtuali per identificare e validare nuovi farmaci in modo più rapido, mirato e sostenibile.
- **Medicina di precisione predittiva:** sviluppo di modelli digitali e biologici per personalizzare le terapie e ridurre sperimentazioni inefficaci.
- **Banca di modelli tumorali:** creazione di una biobanca vivente nazionale, estendibile a livello europeo, per condividere modelli preclinici standardizzati e dati interoperabili.
- **Impatto sul SSN:** infrastruttura dati nazionale che migliora efficienza, sicurezza e accesso alle cure, rafforzando la competitività scientifica del Paese.

What's next

Scaling up the PoC to the national health system

- Involving further hospitals (IRCCS and non)
- Define a national strategy for data transfer, storage, and mining
- Make a homogeneous system for EHR
- Implement next-generation EHR models for omics data
- Create a national organoid biobank for PDAC and other oncology diseases
- Identify innovative targets for anti-cancer drug discovery
- HPC-driven personalized drug discovery and development
- Novel biological and medical discovery exploiting the amount of data generated

ICSC
Centro Nazionale di Ricerca in HPC,
Big Data and Quantum Computing

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MEDICAL & COMPUTATIONAL GENOMICS

Researchers

Manuela Vecchi
Alessandro Coppe
Fabio Landuzzi
Sara Trova

PhD students

Silvia Maria Macrì
Stefano Marangoni
Gaia Mazzocchetti
Fabiana Ferrari

Laboratory technicians

Vittoria Perseghin
Martina Toscano
Alessandro De Filippo
Pariya Kiyashemshaki

Research fellows

Federica Furia
Debora Charrance
Mariantonietta Palazzo
Salvatore Di Dio
Andrè Fiou

IT technicians

Christopher Savin
Marcelo Eduardo Redoschi

ADMINISTRATIVE SUPPORT

Project Management

Alessandra Gastaldi
Emilie Jacquemod
Arianna Torricelli
Axel Bongiovanni

Legal

Antonella Fontana
Marzia Vona
Carlo Tacchino
Arianna De Arcangelis

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BACK UP SLIDE

Retrospective HRC-PDAC cohort