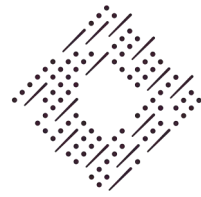




princess
máxima
center
pediatric oncology



**Onco
Accelerator**



UMC Utrecht

Data-driven childhood cancer precision medicine and research

Patrick Kemmeren, PhD

Principal Investigator & head Big Data Core, Princess Máxima Center for Pediatric Oncology

Associate Professor, Center for Molecular Medicine, UMC Utrecht

Childhood cancer

Major cause of disease-related death



Childhood cancer survival rate has increased the last decades to around 75-80% today

Still major cause of disease-related child death in high-income countries



Our mission

To cure every
child with cancer,
with an optimal
quality of life



Our primary use case

Biobank

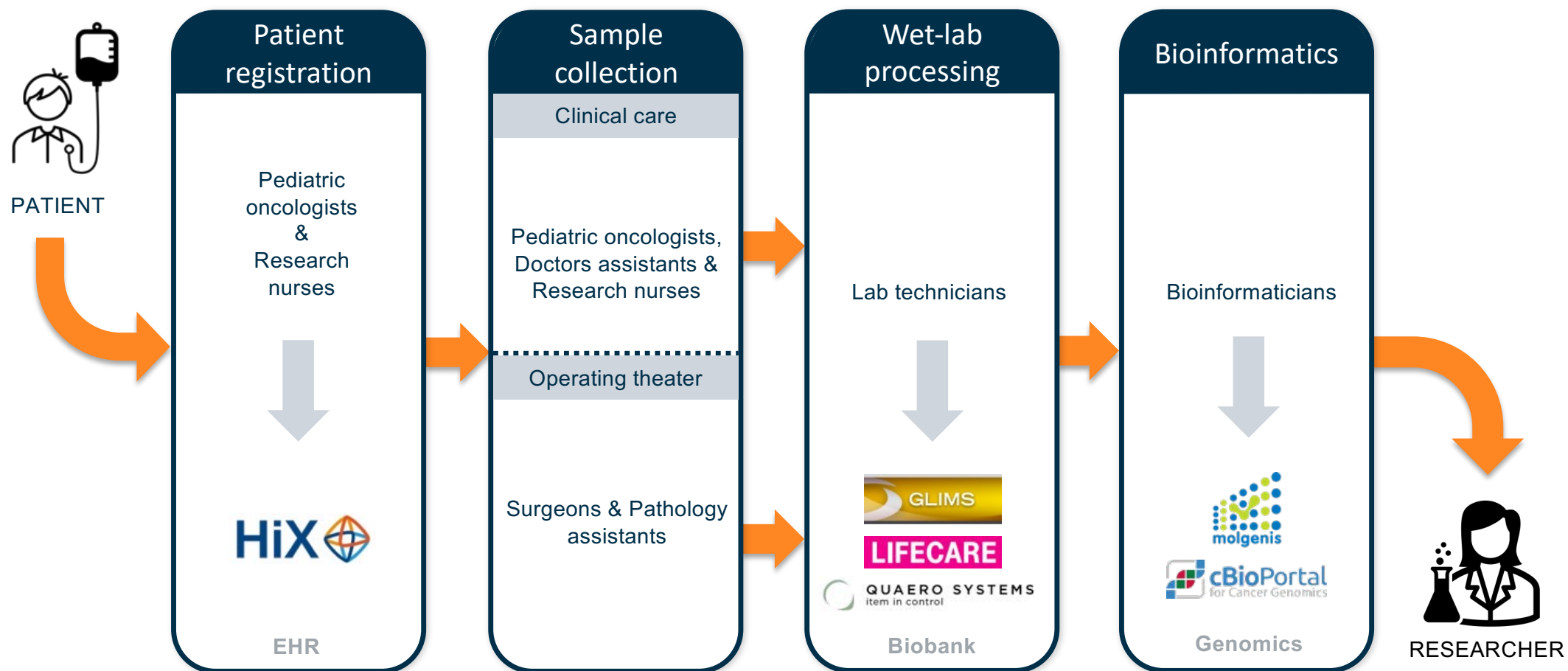
Broad informed consent

Data of 2500 patients,
sequencing (WGS, RNA-seq) for
~900 patients

Biobank & Data Access
Committee (BDAC)

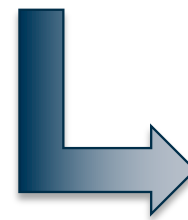
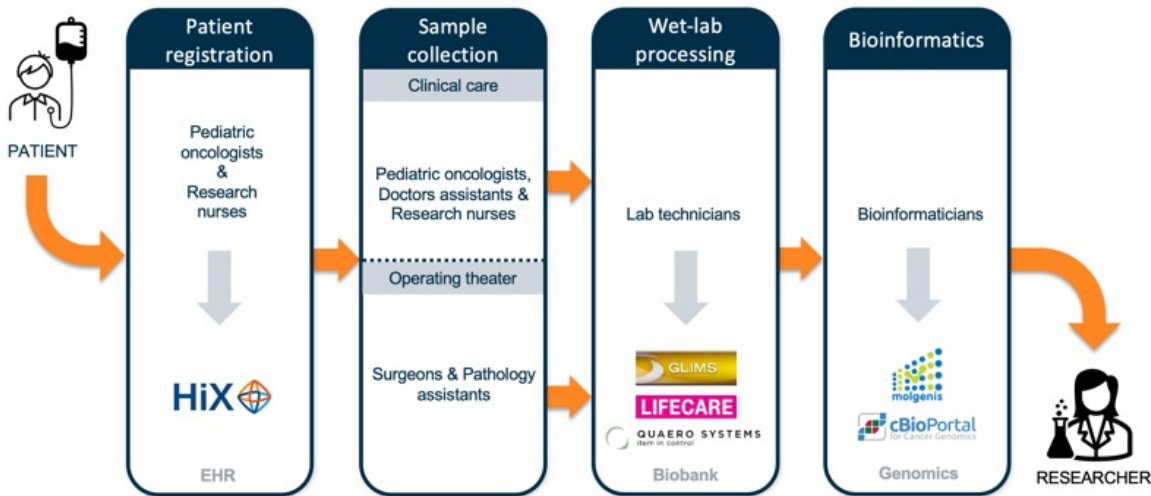


Biobanking flow



Biobanking flow

Sequencing & bioinformatics



Diagnostics

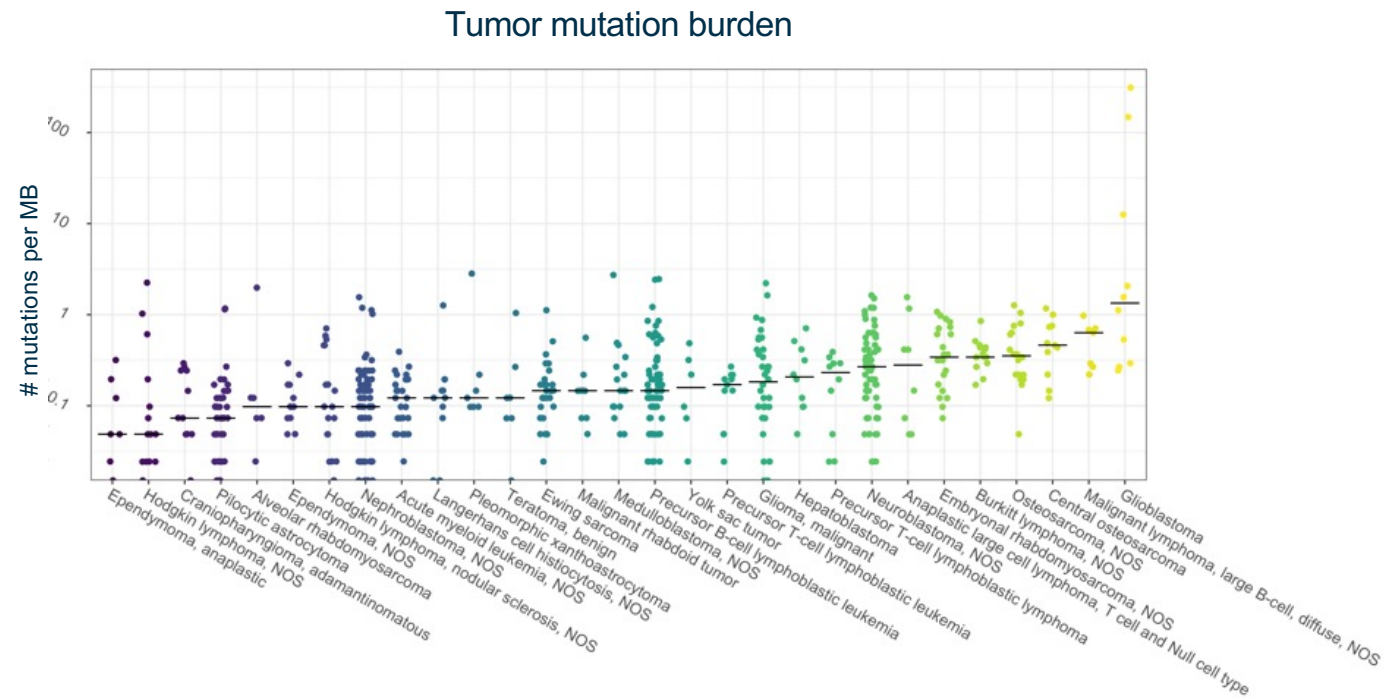
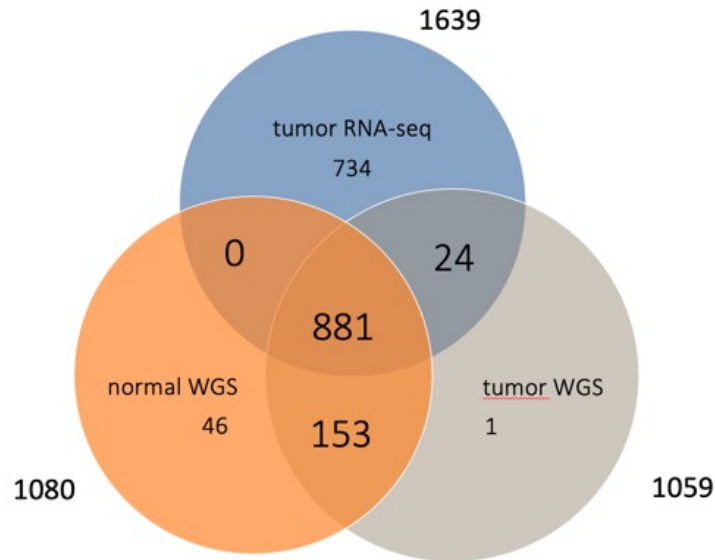
WES
RNA-seq
DNA methylation

Research

WGS
RNA-seq
DNA methylation

Dutch Childhood Cancer Genome Project

Create a uniform and unique data set of WGS + RNA-seq pediatric cancer genomes for research



Joanna von Berg, Ianthe van Belzen, Anastasia Spinou, Fleur Wallis, Hinri Kerstens, Jayne Hehir-Kwa

Máxima cBioPortal

Release v12, April 2024, 2,142 patients



cBioPortal FOR CANCER GENOMICS | Data Sets | Tutorials/Webinars | Logged in as p.kemmeren@prinsesmaximacentrum.nl | Institute Logo

Release 12: 2024 April | This is the 12th Biobank cBioPortal data release. Please be careful with drawing any conclusions based on this dataset without validating your findings.

Selected: 2,142 patients | 2,698 samples | Custom Selection | Charts | Groups

Genomic Profile Sample Counts

Molecular Profile	#	Freq
Mutations	2,698	100.0%
RNA-seq Expression	2,608	96.7%
Structural Variant	2,551	94.6%
CNA ratios	1,516	56.2%
Putative copy-number alterations ...	1,516	56.2%

KM Plot: Os (months)

Number of Samples Per Patient

Mutation Count vs Fraction Genome Altered

Pearson: 0.0105, p=0.67
Spearman: 0.0362, p=0.15

Cancer Type

Cancer Type	#	Freq
Leukemias, myeloproliferative d...	715	26.5%
CNS and miscellaneous intracra...	565	20.9%
Soft tissue and other extraosse...	236	8.7%
Lymphomas and reticuloendoth...	223	8.3%
NA	207	7.7%
Malignant bone tumors	194	7.2%
Neuroblastoma and other perip...	186	6.9%
Renal tumors	159	5.9%
Germ cell tumors, trophoblastic...	99	3.7%
Other malignant epithelial neopl...	56	2.1%
Hepatic tumors	30	1.1%

Cancer Type Detailed

Cancer Type	#	Freq
Precursor B-cell lymphoblastic l...	398	14.8%
Acute myeloid leukemia, NOS (...)	193	7.2%
Pilocytic astrocytoma (C71...)	178	6.6%
Neuroblastoma, NOS	165	6.1%
Nephroblastoma, NOS (C64.9)	132	4.9%
Glioma, malignant (C71...)	115	4.3%
NA	110	4.1%
Ewing sarcoma	77	2.9%
Medulloblastoma, NOS (C71.6)	72	2.7%
Embryonal rhabdomyosarcoma,...	71	2.6%
Precursor T-cell lymphoblastic l...	61	2.3%

Mutated Genes (2698 profiled samples)

Gene	# Mut	#	Freq
MUC4	1,145	651	24.1%
TTN	598	289	10.7%
MUC5AC	346	263	9.7%
UBR4	306	256	9.5%
HMCN1	499	249	9.2%
HLA-A	324	243	9.0%
MUC12	305	226	8.4%
TEX13C	275	226	8.4%
GOLGA6L6	259	222	8.2%
MUC16	451	219	8.1%
HLA-C	303	213	7.9%

Structural Variant Genes (2551 profiled samples)

Gene	# SV	#	Freq
RN7SL2	2,131	1,295	50.8%
USP22	2,226	1,292	50.6%
LINC00630	1,154	1,123	44.0%
RN7SL5P	1,036	1,025	40.2%
SH3BGRL2	1,001	996	39.0%
RN7SK	1,431	744	29.2%
RN7SL1	1,383	698	27.4%
ZEB2	1,095	569	22.3%
PTCHD4	594	567	22.2%
RPPH1	963	547	21.4%
SNORD3A	738	539	21.1%

CNA Genes (1516 profiled samples)

Gene	Cytoband	CNA	#	Freq
RNU1-4	1p36.1	HOMD...	446	29.4%
RNU1-3	1p36.1	HOMD...	446	29.4%
RNU1-1	1p36.13	HOMD...	446	29.4%
RNU1-2	1p36.13	HOMD...	446	29.4%
DEFB130A	8p23.1	AMP	388	25.6%
FAM66A	8p23.1	AMP	382	25.2%
POTEB	15q11.2	AMP	374	24.7%
POTEB2	15q11.2	AMP	374	24.7%
GOLGA8CP	15q11.2	AMP	374	24.7%
NF1P2	15q11.2	AMP	374	24.7%
OR4K2	14q11.2	AMP	373	24.6%

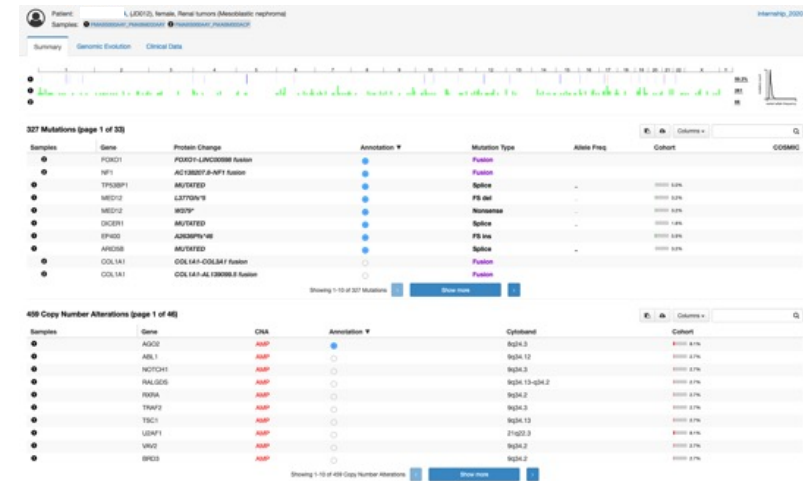
Máxima cBioPortal

Different views on the same data



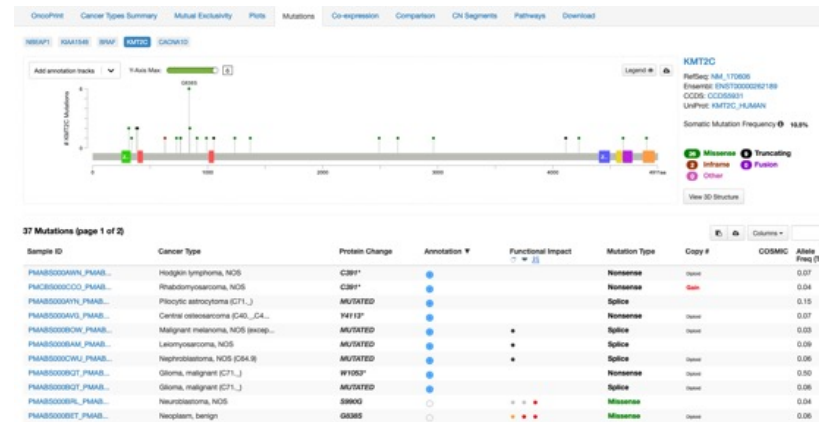
Cohort/study overview

Patient overview

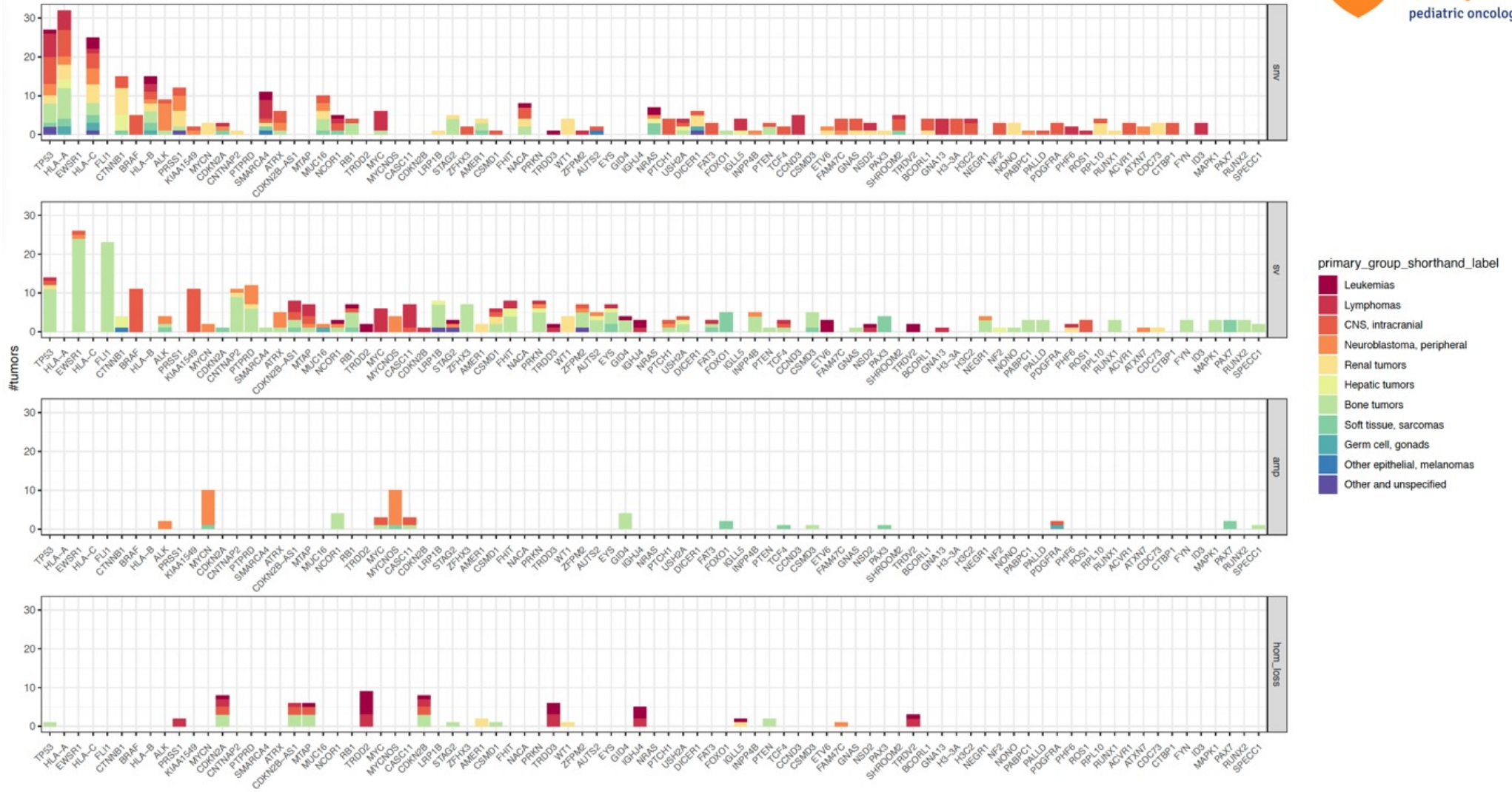


Oncoprint

Gene/mutation level view

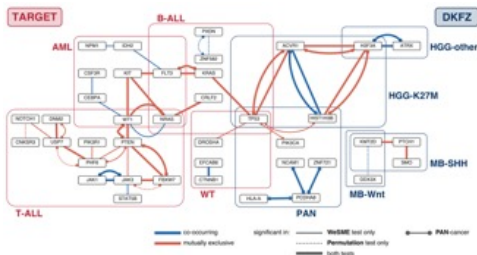


Mutational landscape of childhood cancers



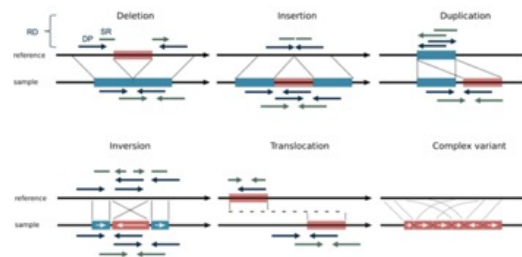
From basic tumor biology to clinical utility

Genetic interactions



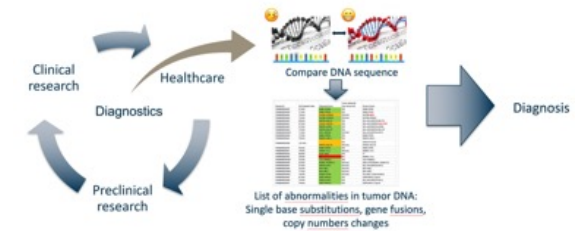
basic research

Structural variation detection



translational research

Translational Bioinformatics

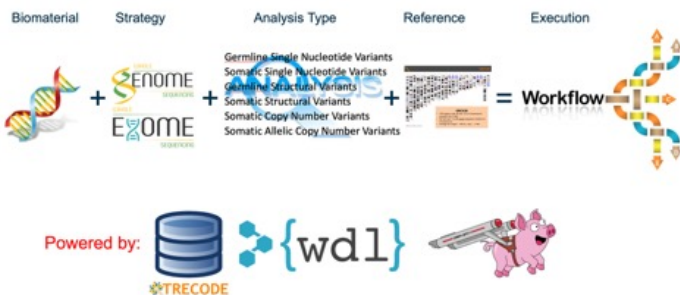


Clinical utility

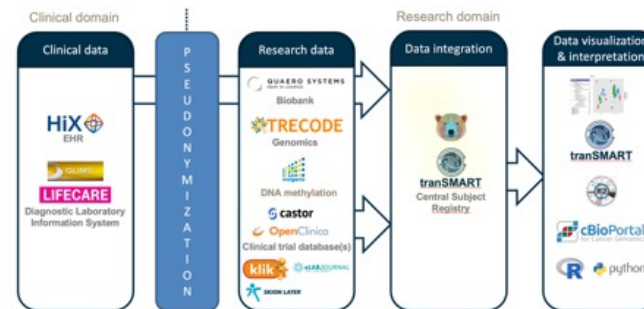


Technology-driven

Biobank Bioinformatics



Data Infrastructure



Data Stewardship




From basic tumor biology to clinical utility



Genetic interactions

Structural variation detection

Translational Bioinformatics



communications biology
ARTICLE
<https://doi.org/10.1038/s43031-021-00414-4> OPEN

A systematic analysis of genetic interactions and their underlying biology in childhood cancer


Josephine T. Dau^{1,5}, Saman Amin^{1,5}, Denise J. E. Kerjens¹, Xiaohu Ma², Natalie Jäger³, Jinghui Zhang², Stefan M. Pfister⁴, Frank C. P. Holstege¹ & Patrick Kemmeren^{1,5}



cancers MDP1

Article
Molecular Characterization Reveals Subclasses of 1q Gain in Intermediate Risk Wilms Tumors

Ilanthe A. E. M. van Belzen¹, Marc van Tuil¹, Shaahi Badloe¹, Eric Strengman^{1,6}, Alex Janse^{1,6}, Eugène T. P. Verwiel^{1,6}, Douwe F. M. van der Leest¹, Sam de Vos¹, John Baker-Hernandez¹, Alissa Groenendijk¹, Ronald de Krijger¹, Hindrik H. D. Kerstens¹, Jarmo Drost^{1,2,6}, Marry M. van den Heuvel-Eibrink^{1,3}, Bastiaan B. J. Tops¹, Frank C. P. Holstege¹, Patrick Kemmeren^{1,4,6} and Jayne Y. Hehir-Kwa^{1,4}



DIAGNOSTICS **Improved Gene Fusion Detection in Childhood Cancer Diagnostics Using RNA Sequencing**

Jayne Y. Hehir-Kwa, PhD¹, Marco J. Kruitwijk, PhD^{1,4}, Eugène T. P. Verwiel, BSc¹, Lennart A. Kester, PhD¹, Marc van Tuil, BSc¹, Eric Strengman, BSc¹, Aljan Buis, PhD¹, Marjolijn E. G. Kraanbroek, PhD¹, Laura S. Hemscho-Java, PhD¹, Valerie de Haas, PhD¹, Ellen van de Geer, BSc¹, Wendy de Krom, PhD¹, Jinger van der Lugt, PhD¹, Philip Lijssens, PhD¹, Frank C. P. Holstege, PhD¹, Patrick Kemmeren, PhD¹ and Bastiaan B. J. Tops, PhD¹

basic research

translational research

Clinical utility



Technology-driven

Biobank Bioinformatics

Data Infrastructure

Data Stewardship



Trecode: a FAIR eco-system for the analysis and archiving of omics data in a combined diagnostic and research setting

Hindrik HD Kerstens, Jayne Y Hehir-Kwa, Ellen van de Geer, Chris van Run, Eugène TP Verwiel, Douwe van der Leest, Bastiaan BJ Tops, Patrick Kemmeren



RNA-seq gene fusion detection for precision oncology & precision medicine



Hehir-Kwa, Koudijs et al, JCO Prec Onc 2022

DIAGNOSTICS

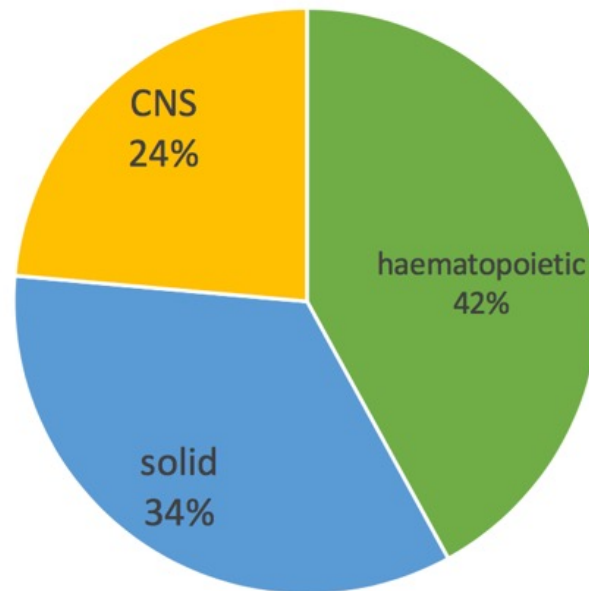
Improved Gene Fusion Detection in Childhood Cancer Diagnostics Using RNA Sequencing

Jayne Y. Hehir-Kwa, PhD¹; Marco J. Koudijs, PhD^{1,2}; Eugene T. P. Verwiel, BSc¹; Lennart A. Kester, PhD¹; Marc van Tuil, BSc¹; Eric Strengman, BSc¹; Arjan Buijs, PhD²; Mariëtte E. G. Kranendonk, PhD¹; Laura S. Hiemcke-Jiwa, PhD¹; Valerie de Haas, PhD¹; Ellen van de Geer, BSc¹; Wendy de Leng, PhD³; Jasper van der Lugt, PhD¹; Philip Lijnzaad, PhD¹; Frank C. P. Holstege, PhD¹; Patrick Kemmeren, PhD¹; and Bastiaan B. J. Tops, PhD¹

Jayne Hehir-Kwa, Marco Koudijs, Bas Tops

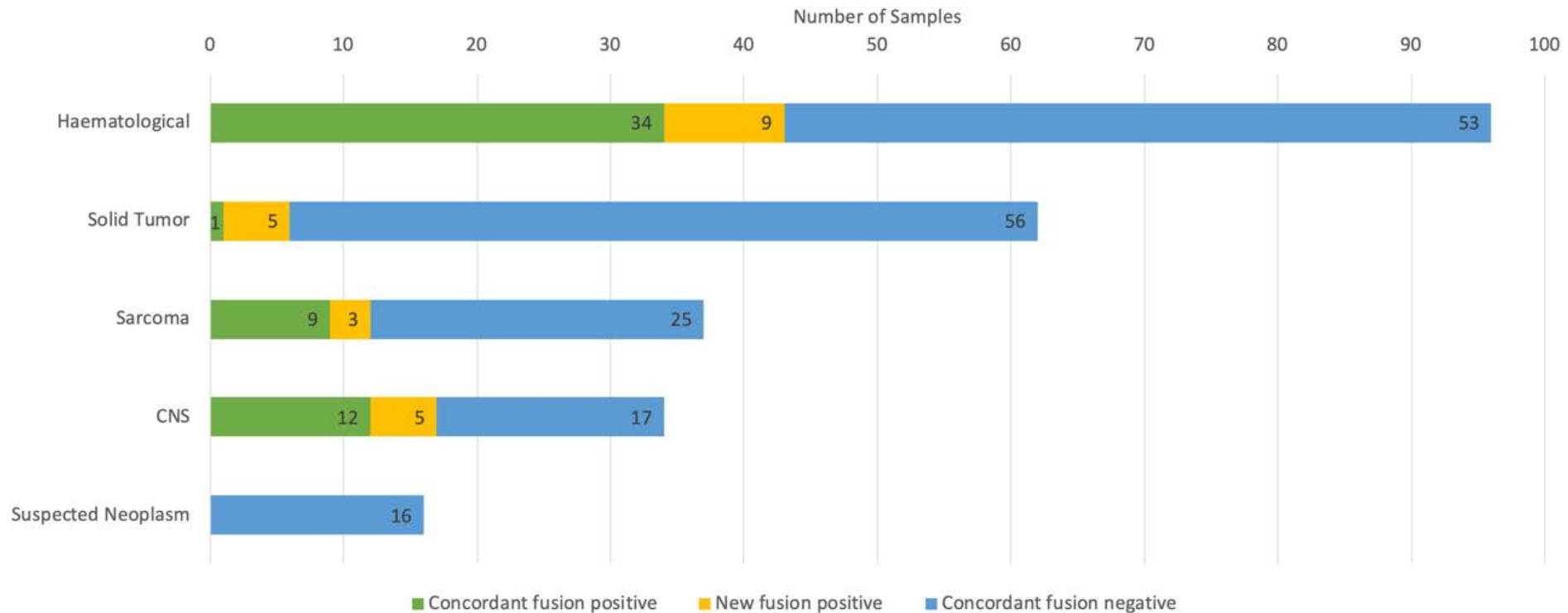
RNA-seq gene fusion detection in diagnostics

257 consecutive patients from 1st December 2018 until 31 May 2019



RNA-seq gene fusion detection in diagnostics

Increased sensitivity of clinically relevant events



No events missed

>40% increase in clinically relevant events (22% → 36%)

RNA-seq gene fusion detection in diagnostics

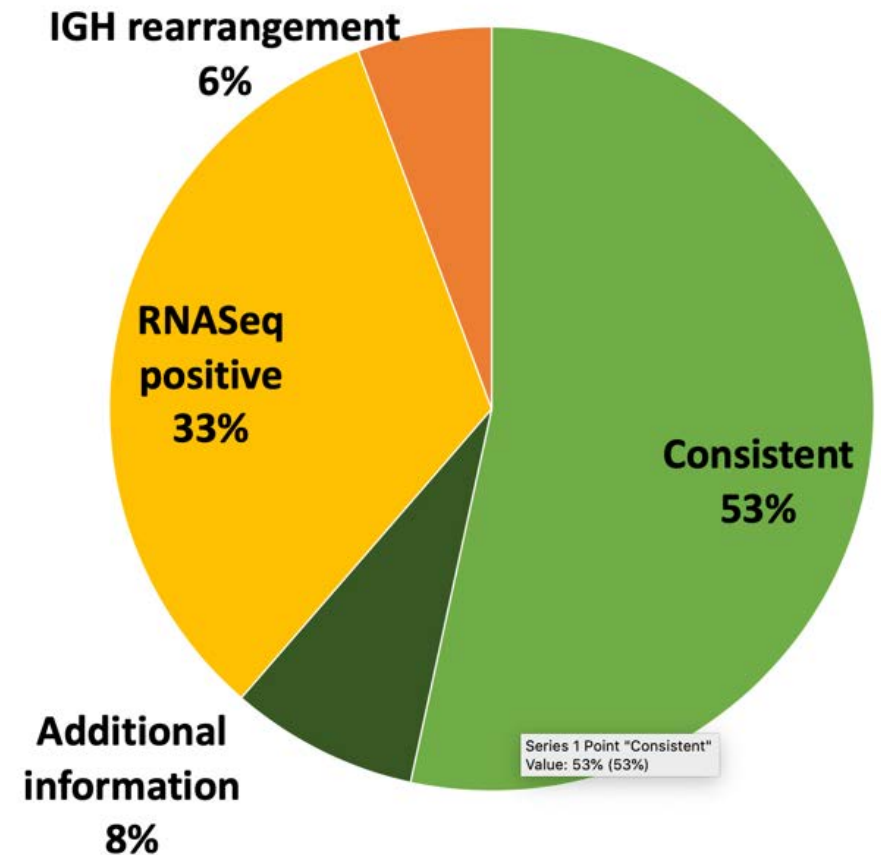
The fusion positive cases

Additional information

- Fusion partner
- More accurate breakpoint

Additional events

- Not tested
- Atypical breakpoints
- IGH rearrangements



RNA-seq gene fusion detection in diagnostics

The fusion positive cases

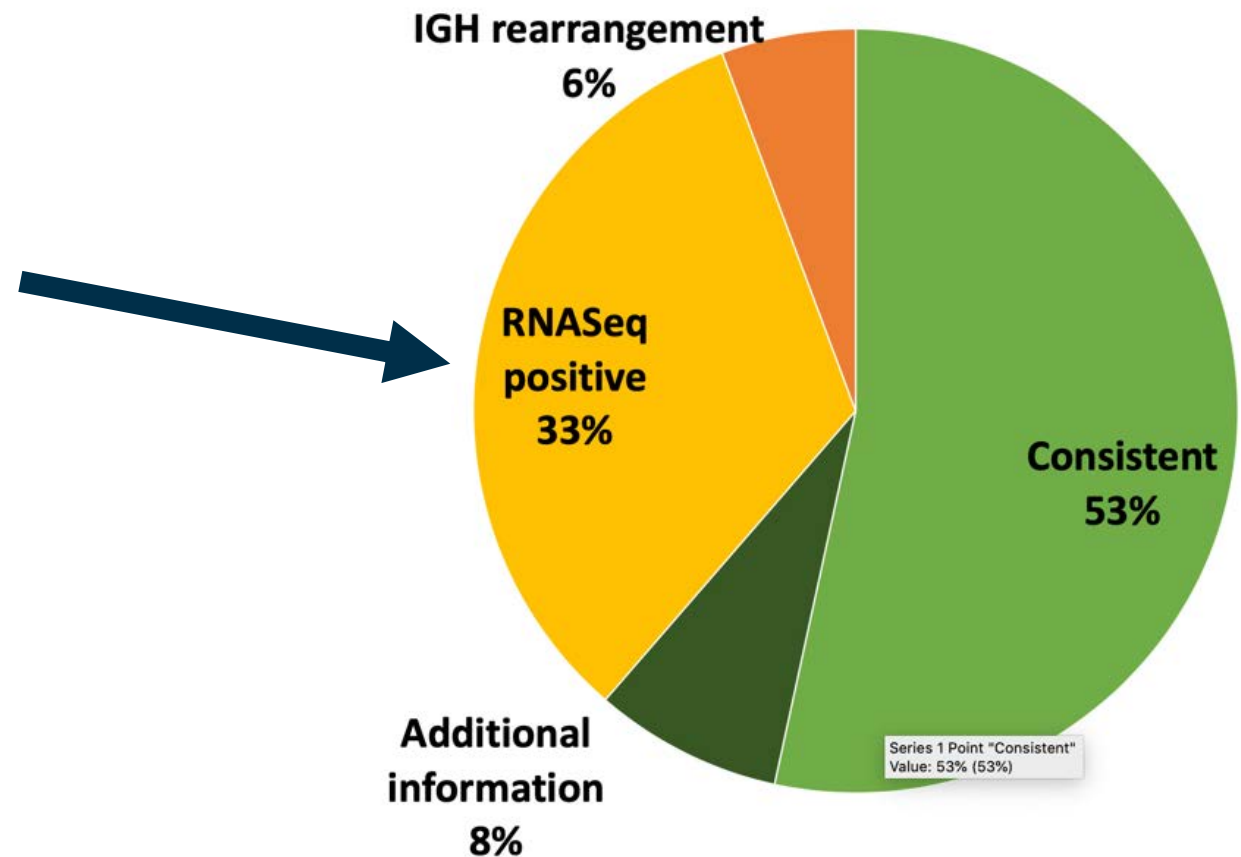
4 new druggable gene fusions

ZCCHC8-ROS1

PPP1CB-ALK

EML4-ALK

EML4-NTRK3



Acknowledgements



UMC Utrecht



Parents & children

Kemmeren lab & Big Data Core

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Fleur Wallis

Carolina Pita Barros

Emma Bernsen

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Hinri Kerstens

Alex Janse

John Baker-Hernandez

Sam de Vos

Jet Zoon

Marcel Santoso

Victoria Cruz

Sotiris Niarchos

Richard Gremmen

Shashi Badloe

Kim Verhagen

Josephine Daub

Denise Kersjes

Saman Amini

Diagnostic lab

Bas Tops

Marco Koudijs

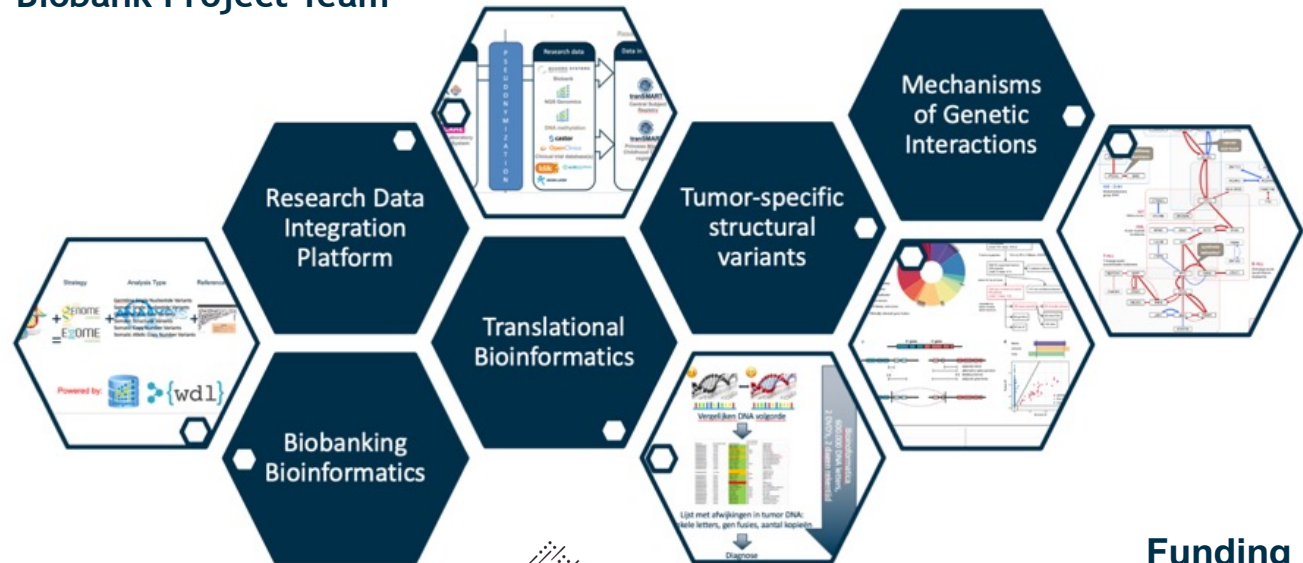
Marc van Tuijl

Lennart Kester

Trial & Data Centrum

IDT

Biobank Project Team



Utrecht
Bioinformatics
Center



ADESIUM
FOUNDATION

Funding

