In the Name of God

Genomics in Pediatric Sarcoma Treatment

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Pediatrician & Medical Geneticist

IUMS

Outline

- Precision Oncology
- Genomics vs Epigenomics
- Genomic Profile vs Genetic Profile
- Integrated Genomics/ICS/IGS
- Somatic vs Germline
- STS vs Bone Sarcoma
- Pediatrics vs Adult
- Treatment vs Diagnosis & Prognosis
- Guidelines

Precision Oncology

- The aim: identify actionable gene alterations, enabling personalized precision medicine for cancer patients.
- Omics
- Integrated Genomics / IGS/ ICS:
  - WGS
  - WES/ Targeted NGS Panels
  - RNASeq

CA: A Cancer Journal for Clinicians
The flagship journal of the American Cancer Society

Article | Open Access

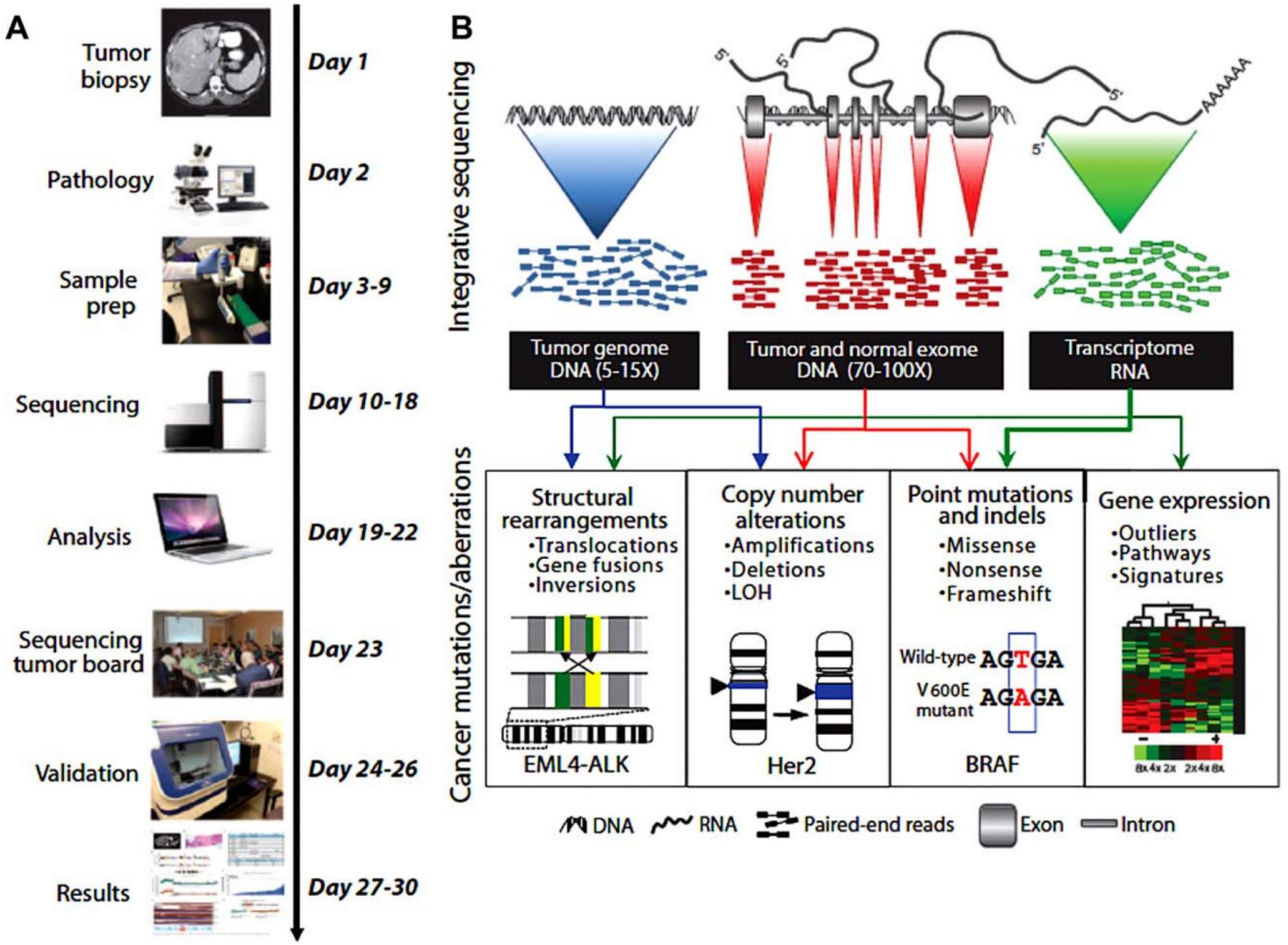
Translating cancer genomes and transcriptomes for precision oncology

Sameek Roychowdhury MD, PhD, Arul M. Chinnaiyan MD, PhD

CA CANCER J CLIN 2016;66:75–88

Translating Cancer Genomes and Transcriptomes for Precision Oncology

Sameek Roychowdhury, MD, PhD[1,2,3]; Arul M. Chinnaiyan, MD, PhD[4,5,6,7,8,9]



Tumor-site agnostic:
Mutation-based & Pathway-based Basket
Pan-Cancer Approach

CA CANCER J CLIN 2016;66:75–88

Translating Cancer Genomes and Transcriptomes for Precision Oncology

Sameek Roychowdhury, MD, PhD[1,2,3]; Arul M. Chinnaiyan, MD, PhD[4,5,6,7,8,9]

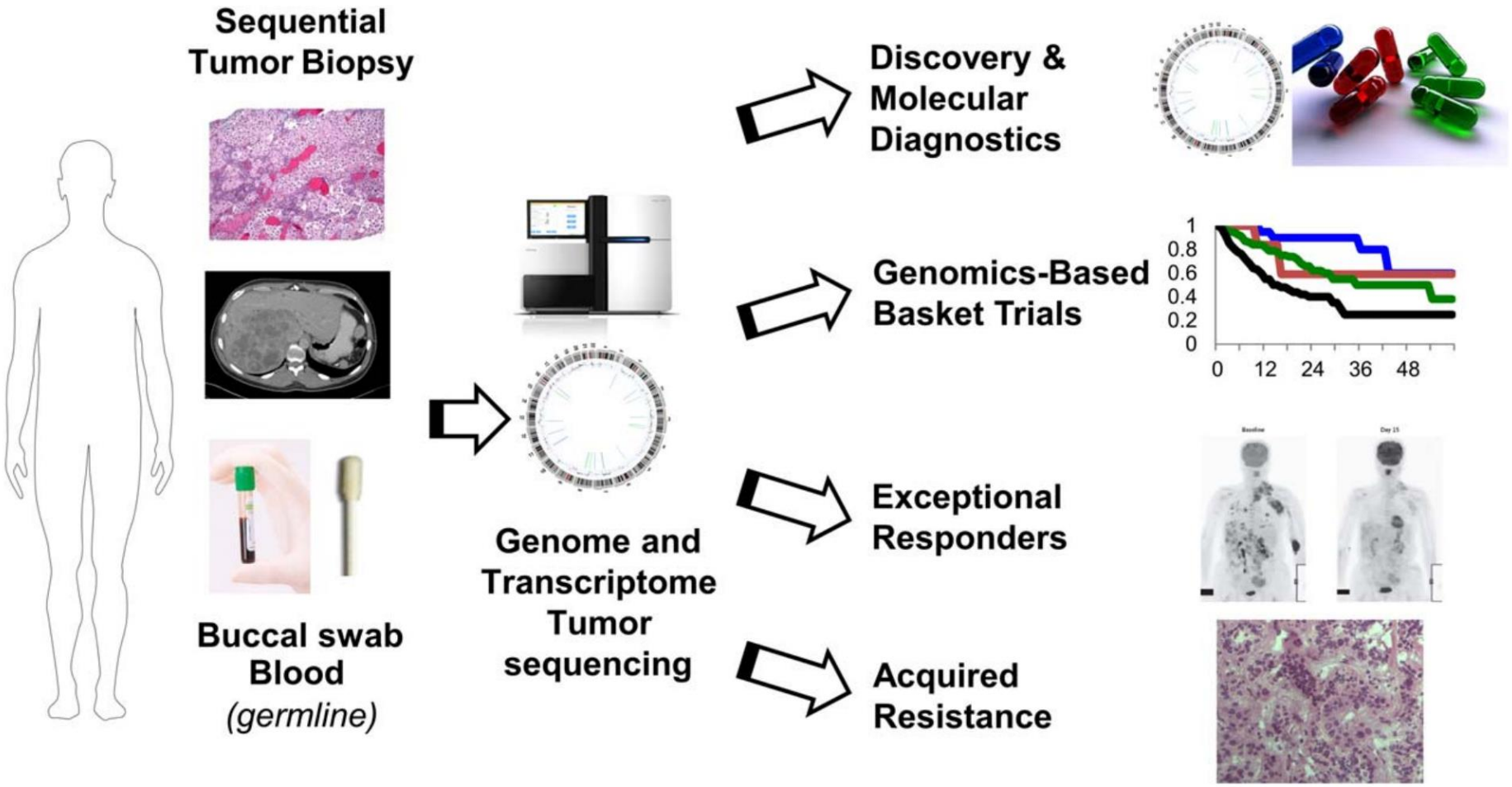


TABLE 1. Commercial Targeted DNA Pan-Cancer Next-Generation Sequencing Assays

VENDOR	ASSAY NAME	NO. OF GENES	RESULTS	ESTIMATED TURNAROUND TIME
Foundation Medicine (Cambridge, MA)	Foundation One	315	SNVs, CNVs, fusions	12-14 days
University of Washington (Seattle, WA)	UW-Oncoplex	234	SNVs, CNVs, fusions	6 weeks
Paradigm (Ann Arbor, MI)	PCDx	114	SNVs, CNVs, fusions	4-5 days
Genomics and Pathology Services, Washington University School of Medicine (St. Louis, MO)	Solid Tumor Gene Set	48	Hot-spot mutations, 6 fusions	3 weeks
ARUP Laboratories (Salt Lake City, UT)	Solid Tumor Mutation Panel	48	Hot-spot mutations	14 days
Caris Life Sciences (Irving, TX)	MI Profile	46	Hot-spot mutations	14 days
Knight Diagnostic Laboratories (Portland, OR)	GeneTrails Solid Tumor Panel	37	Hot-spot mutations	10-14 days

CNVs indicates copy number variations; SNVs, single nucleotide variations or point mutations. Gene content is subject to change with additional content added over time.

Simon *et al. BMC Cancer* (2024) 24:1296
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BMC Cancer

RESEARCH Open Access

Clinical impact of large genomic explorations at diagnosis in 198 pediatric solid tumors: a monocentric study aiming practical feasibility of precision oncology

Juliette Simon[1], Damien Reita[2,3], Eric Guerin[2,3], Benoit Lhermitte[3,4,5], Noelle Weingertner[4], François Lefebvre[6], Marie Karanian[7], Julien Masliah-Planchon[8], Veronique Lindner[4], Alina Onea[4], Sarah Jannier[1], Alexandra Salmon[1], Guillaume Bergthold[1], Florence Vincent[1], Marlène Deschuyter[3], Marie-Odile Barbaza[9] and Natacha Entz-Werlé[1,3*]

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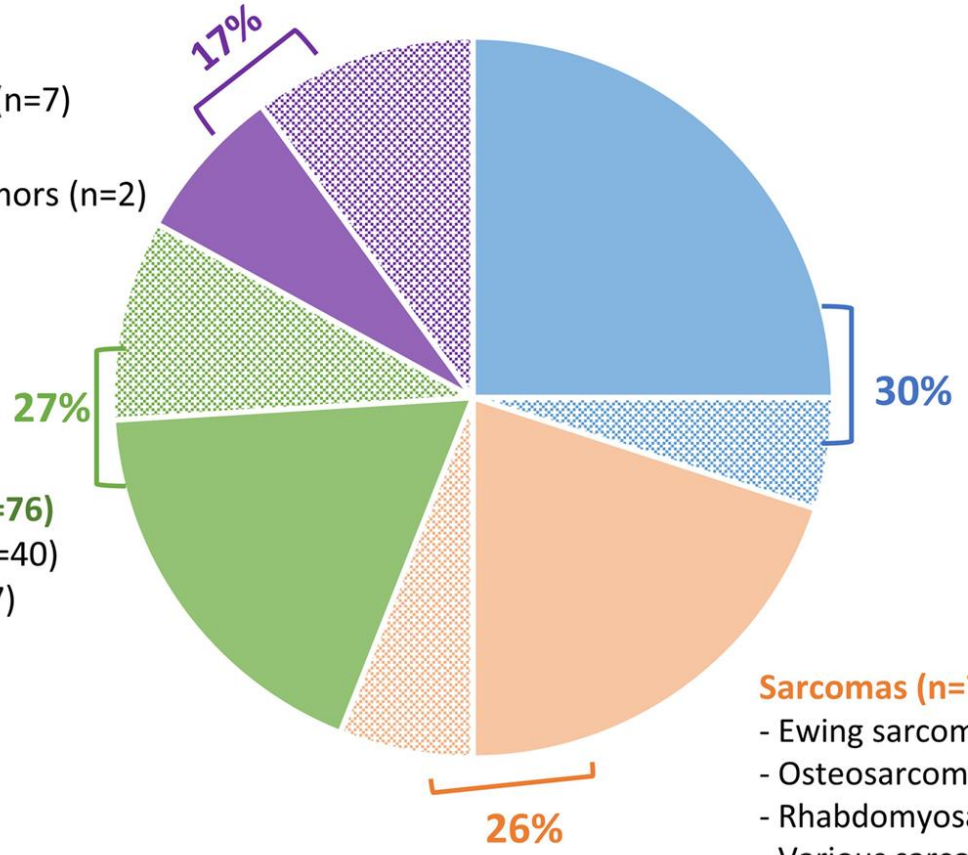
Methods (Simon, J. et al. 2024)

- A total of 280 patients less than 22 years, referred at the University Hospitals of Strasbourg for a newly diagnosed solid tumor from January 2015 to December 2021.
- Using 7 different molecular tests going from
  - single-gene methods (IHC, FISH, RT-PCR, Sanger sequencing, droplet digital PCR)
  - largescale analyses (Next-Generation sequencing, RNAsequencing and FoundationOne®CDx)

Results (Simon, J. et al. 2024)

Other tumors (n=48)
- Germ line tumors (n=21)
- Carcinomas (n=8)
- Neuroendocrine tumors (n=7)
- MPNST tumors (n=6)
- Extracranial rhabdoid tumors (n=2)
- Melanoma (n=1)



CNS tumors (n=86)
- **Glial tumors (n=53):**

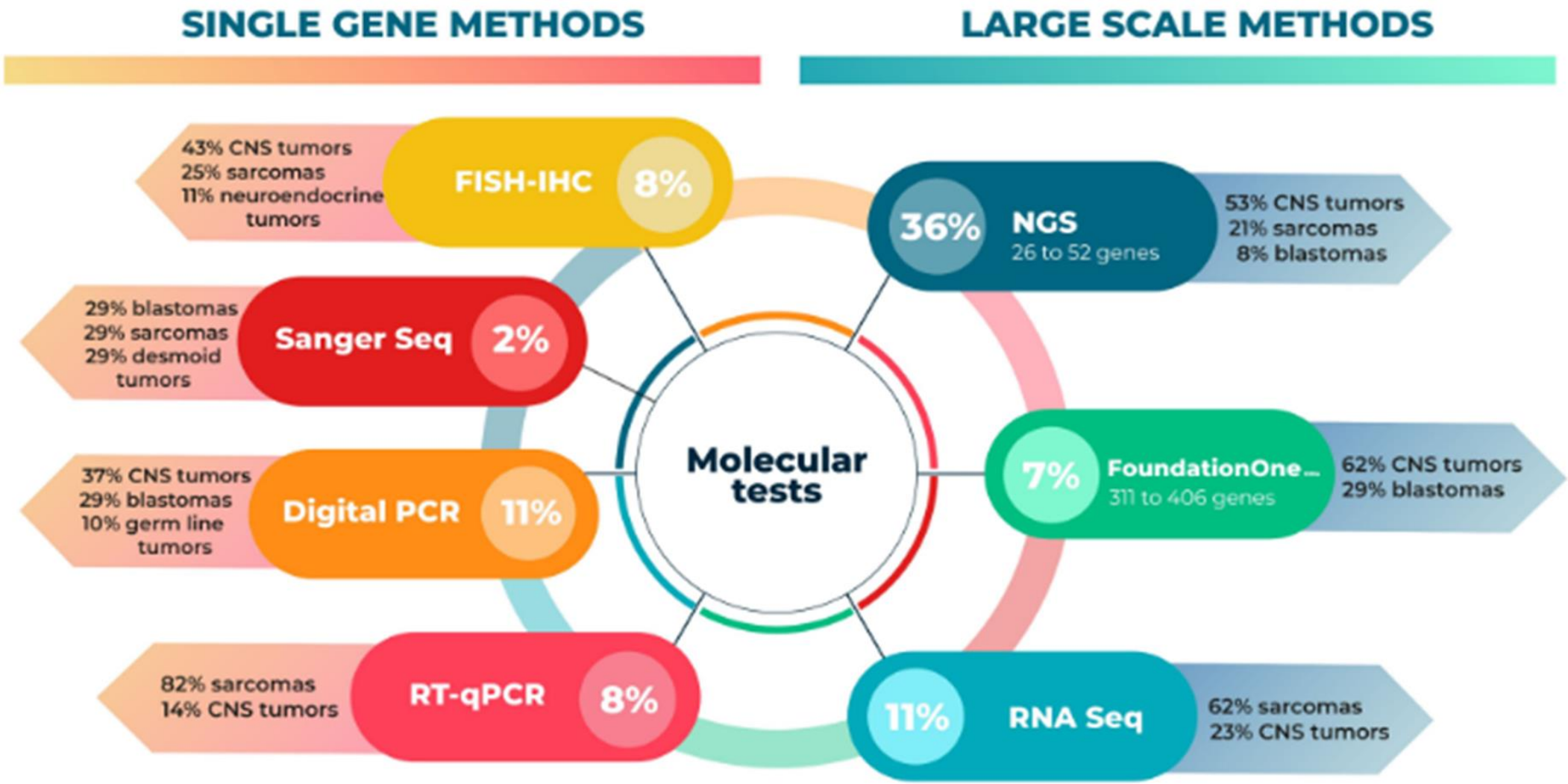
Ependymomas (n=6)
Low grade (I/II):
*Pilocytic astrocytomas (n=19)
*Gangliogliomas (n=14)
High grade (III/IV):
*Anaplastic astrocytomas (n=4)
*High-grade gliomas (n=6)
*DIPG (n=4)
- **Embryonal tumors (n=21):**
  - Medulloblastomas (n=16)
  - ATRT (n=5)
- **Other tumors (n=12)**

Malignant blastomas (n=76)
- Neuroblastomas/GN (n=40)
- Nephroblastomas (n=17)
- Retinoblastomas (n=10)
- Hepatoblastomas (n=9)

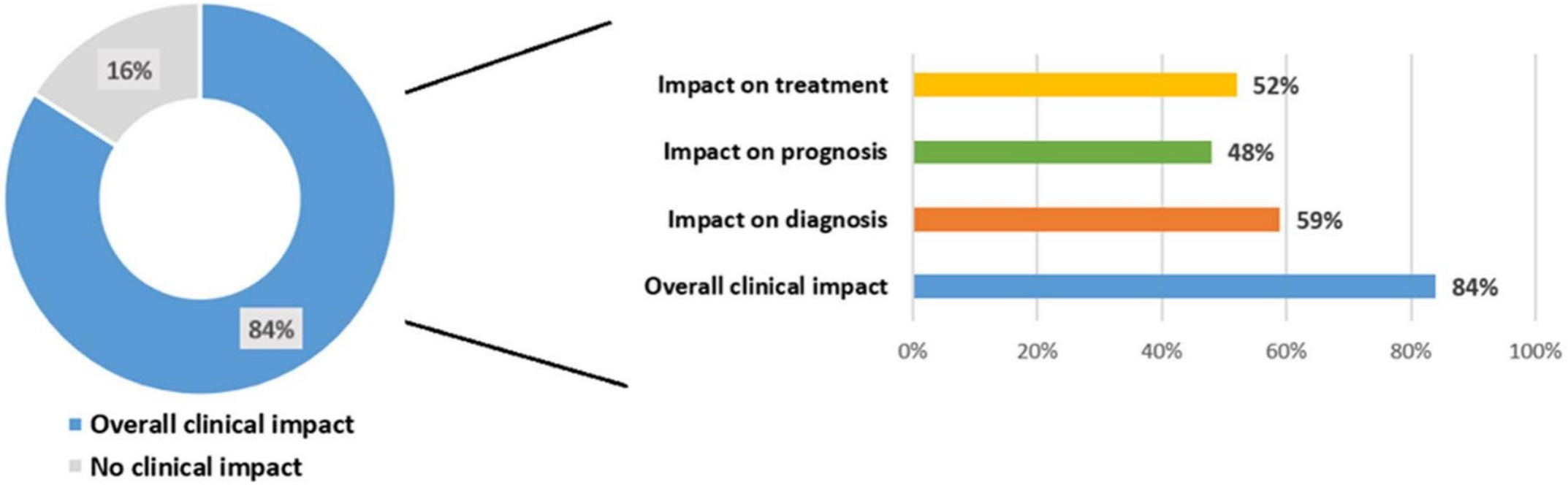
Sarcomas (n=74)
- Ewing sarcomas (n=22)
- Osteosarcomas (n=21)
- Rhabdomyosarcomas (n=15)
- Various sarcomas (n=10)
- Desmoid/desmoplastic tumors (n=6)

proportion with MB
proportion without MB

Results (Simon, J. et al. 2024)

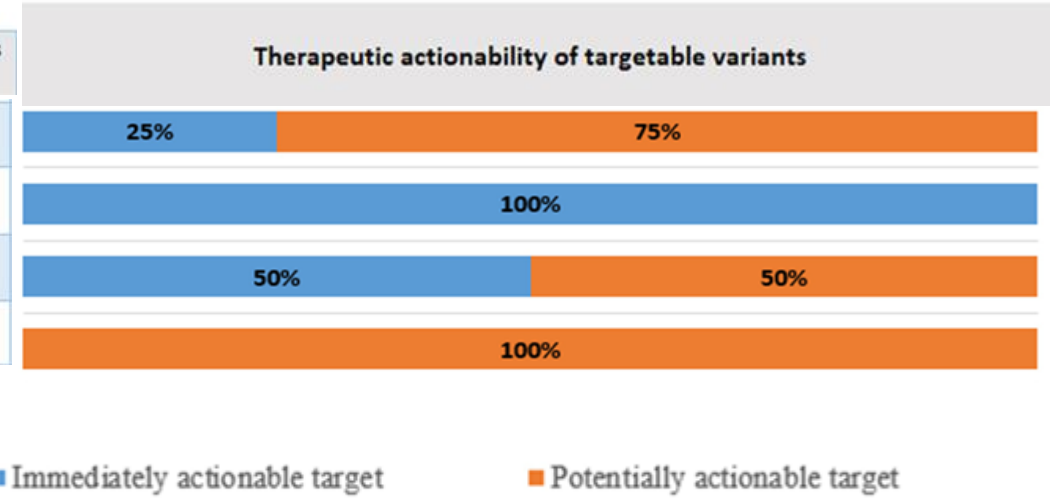


Results (Simon, J. et al. 2024)



Results (Simon, J. et al. 2024)

	Histologies of interest	Number of variants	Targetable variants proportion (%)
Soft-tissue sarcoma	Non-RMS soft-tissue sarcomas (n=11)	13	30%
	Rhabdomyosarcomas (n=15)	8	12%
Bone sarcoma	Ewing sarcomas (n=21)	26	15%
	Osteosarcomas (n=9)	4	75%



Results (Simon, J. et al. 2024)

- Individual test performance, illustrated by at least one observed variant, reached 90% for FoundationOne®CDx (19/21 tests), 76% for RNAseq (29/38), and 56% for NGS (68/121).
  - As expected, broad-spectrum analyses showed a better ability to detect alterations than the targeted tests (74% *versus* 58% of positivity)
- By detailing performances,
  - RNAseq had a better diagnostic performance,
  - FoundationOne®CDx a better prognostic performance, and
  - therapeutic actionability was similar for NGS and FoundationOne®CDx testing (around 65%)

Discussion (Simon, J. et al. 2024)

- Sarcomas, were benefiting from almost all techniques depending on the study time and the mutations/fusions' discovery
- The poor genomic results in osteosarcomas suggest the potential necessity of specific panels by histology or the use of systematic broader sequencing technique in all patients (exome and RNAseq) or using dedicated epigenetic approaches in sarcomas to pick up the specific targets
- **Conclusion**
  - Clinical utility of molecular profiling of solid tumors as soon as at diagnosis in children
    - to expect improving access to innovative agents at relapse.

cancers 2021 MDPI

Article

Clinical Value of NGS Genomic Studies for Clinical Management of Pediatric and Young Adult Bone Sarcomas

Miriam Gutiérrez-Jimeno [1], Piedad Alba-Pavón [2], Itziar Astigarraga [2,3], Teresa Imízcoz [4], Elena Panizo-Morgado [1], Susana García-Obregón [2], Ana Catalán-Lambán [1], Mikel San-Julián [5], José M. Lamo-Espinosa [5], Aizpea Echebarria-Barona [2,3], Marta Zalacain [1,6], Marta M. Alonso [1,6] and Ana Patiño-García [1,6,*]

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Clinical characteristics of 53 patients with sarcoma.

Characteristic	Number (%)
Median age at diagnosis (range)	11.8 (0–30.8)
Gender	
Male	30 (56.6)
Female	23 (43.4)
Ethnic origin	
European	47 (88.6)
Latin	3 (5.7)
African	3 (5.7)
Classification of the sarcoma	
Osteosarcoma	25 (47.2)
Ewing's sarcoma	16 (30.2)
Other	12 (22.6)

2.3. NGS Library Preparation and Sequencing

Tumor profiling to detect sequence alterations and abnormal gene fusions was undertaken using the Oncomine™ Childhood Cancer Research Assay (Thermo Fisher, A36486) according to the manufacturer's protocol. This tool analyzes the mutational state of 200 genes, including 82 mutation hotspots, 24 CNV targets, 44 genes with full exome coverage (specifically tumor suppressor genes), and an RNA panel for 97 genes (with >1700 fusion isoform variants).

DNA and RNA libraries were generated using Ion AmpliSeq Library Preparation on the Ion Chef System (Thermo Fisher). Complementary DNA (cDNA) synthesis prior to library preparation for the RNA panel was carried out using SuperScript™ VILO™ Reverse Transcriptase (Thermo Fisher). Sequencing was performed using the 540 chips on the Ion Torrent S5 (Thermo Fisher).

Results (Gutiérrez-Jimeno M, et al 2021)

- In 44 (83%) of the 53 patients, at least one genetic alteration was identified.
- In 80% of these patients, the diagnosis was obtained (*n* = 11) or changed (*n* = 9), and thus genomic data affected therapy.
- The most frequent initial misdiagnosis was Ewing's sarcoma, instead of myxoid liposarcoma (*FUS-DDDIT3*), rhabdoid soft tissue tumor (*SMARCB1*), or angiomatoid fibrous histiocytoma (*EWSR1-CREB1*).
- Two patients had a genetic alteration with an FDA-approved targeted therapy, and 30% had at least one potentially actionable alteration.
- NGS-based genomic studies are useful and feasible in diagnosis and clinical management of pediatric sarcomas.

Table 2. Potentially actionable alterations identified by OncoKB in 53 sarcomas.

Gene	Type of Alteration	*N* Cases	OncoKB Level	Drugs
NF1	**Truncating mutation**	**1**	**Level 1**	**Selumetinib**
ETV6-NTRK3	**Fusion**	**1**	**Level 1**	**Larotrectinib**
CDK4	**Amplification**	**2**	**Level 2B**	**Palbociclib, abemaciclib**
KIT	Amplification	5	Level 3B	Imatinib, sunitinib, regorafenib, ripetrinib
PDGFRA	Amplification	4	Level 3B	Imatinib, sunitinib
BRAF	Fusion	3	Level 3B	Cobimetinib, trametinib
IDH1	Mutation missense	1	Level 3B	Ivosidenib
MET	Amplification	1	Level 3B	Cabozantinib, crizotinib
FLI1	Fusion	14	Level 4	TK216
PTEN	Deletion/Truncating mutation	5	Level 4	AZD8186, GSK2636771
CDKN2A	Deletion/Truncating mutation	4	Level 4	Abemaciclib, ribociclib, palbociclib
FGFR1/FGFR3	Amplification	4	Level 4	AZD4547, erdafitinib, BGJ398, Debio1347
SMARCB1	Fusion/Truncating mutation	2	Level 4	Tazemetostat

The first 3 bolded rows highlight the only three cases with direct treatment indication according to evidence level <3.

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ESMO OPEN SCIENCE FOR OPTIMAL CANCER CARE

ORIGINAL ARTICLE

The role of whole-genome sequencing for guiding systemic therapy in patients with soft tissue sarcoma

P. van der Laan[1,2], W. J. van Houdt[1], H. van Boven[3], P. Snaebjornsson[3,4], L. J. W. Bosch[3], K. Monkhorst[3], Y. M. Schrage[1], L. Heimans[2], J. M. Kerst[2], N. Steeghs[2] & W. T. A. van der Graaf[2,5*]

Departments of [1]Surgical Oncology; [2]Medical Oncology; [3]Pathology, Netherlands Cancer Institute, Amsterdam, the Netherlands; [4]Faculty of Medicine, University of Iceland, Reykjavik, Iceland; [5]Department of Medical Oncology, Erasmus MC Cancer Institute, Rotterdam, the Netherlands

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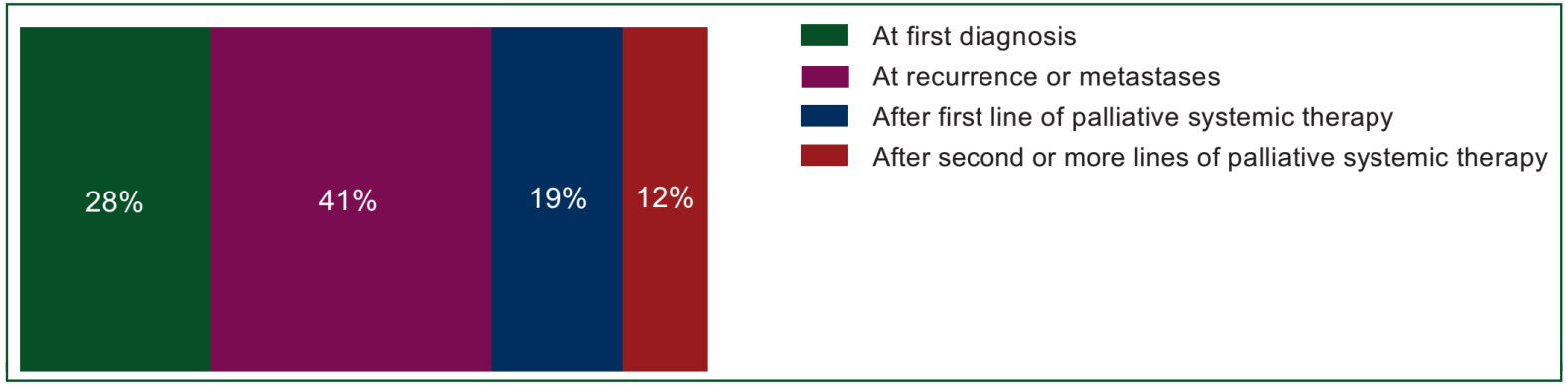
Table 1. Baseline characteristics of patients with soft tissue sarcoma for which whole-genome sequencing was carried out

Patient characteristics	All patients (n = 161)	
	n	%
Median age at diagnosis, years (IQR)	56 (46-65)	
Sex		
Male	84	52
Female	77	48
FNCLCC grade		
1	12	7
2	54	34
3	48	30
Not available or applicable	47	29
Histological tumor type		
Leiomyosarcoma	36	22
UPS/sarcoma NOS	28	17
Dedifferentiated liposarcoma	22	14
Other	75	47
Disease stage at WGS		
Localized	34	21
Locally advanced	22	14
Metastatic	105	65



- At least one actionable target was found by WGS in 74 (46%) of patients.
- Actionable targets were more frequently seen for complex genome sarcomas compared with simple genome sarcomas (50% versus 28%).
- 23 patients (14%) received matched experimental therapy based on their WGS results.
  - Non-availability of WGS directed treatment or lack of clinical necessity for systemic therapy (n= 17) and rapid disease progression causing poor performance score (n= 10) were the main reasons to not start WGS-informed therapy
  - Improving the timing of the WGS request and a more appropriate patient selection upfront could increase this relatively low percentage.
- Complex genome sarcomas seem to be the STS group for which WGS is most likely to add value by opening the way to tumor-agnostic therapies.

www.nature.com/bjc British Journal of Cancer

ARTICLE OPEN

Check for updates

Genetics and Genomics

Introduction and impact of routine whole genome sequencing in the diagnosis and management of sarcoma

James A. Watkins[1,2✉], Jamie Trotman[1], John A. Tadross[1,2,3], Jennifer Harrington[4], Helen Hatcher[4], Gail Horan[4], Sarah Prewett[4], Han H. Wong[4], Sarah McDonald[2], Patrick Tarpey[1], Thomas Roberts[1], Jing Su[1], Marc Tischkowitz[5], Ruth Armstrong[5], Fernanda Amary[6] and Alona Sosinsky[7]

East Genomics Laboratory Hub, Cambridge University Hospitals NHS Foundation Trust, **Cambridge, UK.**

Methods: Introduction of WGS as a diagnostic standard for all eligible patients with known or suspected soft tissue sarcoma over a 2-year period at a soft tissue sarcoma treatment centre.

Inclusion criteria were: any patient 16 years of age or over with either a known or suspected sarcoma of either bone, soft tissue or visceral organ site.

- **Results:** WGS resulted in a refinement in the diagnosis in 37% of cases, identification of a target for personalised therapy in 33% of cases, and a germline alteration in 4% of cases.
- **Conclusion:** Introduction of WGS poses logistical and training challenges, but offers significant benefits to this group of patients.
  - However WGS does have some limitations, and additional genome-wide assays can supplement WGS and provide a more complete molecular portrait of sarcomas.
  - These include
    - long-read sequencing (to assess long-range or poorly mapped SVs and also provide insight into the phase of alterations),
    - methylome sequencing (to assess gene silencing as a second hit on tumour suppressor genes and utilise methylation signature diagnostic classifiers) and
    - transcriptomics (to assess the RNA consequences of complex DNA rearrangements).

Table 1. WGS refined diagnoses

Case	Pre-WGS diagnosis	Selected key diagnostic drivers	Post-WGS integrated diagnosis
1	Recurrent Wilm's tumour vs undifferentiated sarcoma (radiation-related)	HomDels of *ATRX*, *RAD51* Absence of typical WT drivers [41]	Undifferentiated sarcoma
4	Favour dedifferentiated gastrointestinal stromal tumour (GIST) (DOG1+)	4q Amplification (*KIT/NRAS/PDGFRA*) and *MDM2* amplification Absence of typical GIST drivers [42]	Favour undifferentiated sarcoma
5	Leiomyosarcoma	Amplification of *MDM2/CDK4* and *JUN* [43]	Dedifferentiated liposarcoma
7	Cellular schwannoma vs malignant peripheral nerve sheath tumour (MPNST)	*SOX10* Indel [44] Absence of typical MPNST/eMPNST drivers [45, 46]	Cellular schwannoma
9	Malignant meningioma	*YAP1::KMT2A* fusion [47]	KMT2A-rearranged sarcoma
11	Recurrent metaplastic breast carcinoma vs undifferentiated sarcoma	4q Amplification (*KIT/NRAS/PDGFRA*) [25] + novel *TP53* mutation Absence of *TP53* mutation found in previous primary or other small drivers common in breast carcinoma	Undifferentiated sarcoma
14	Low-grade mesenchymal soft tissue neoplasm, favouring plexiform fibromyxoma	*ACTB::GLI1* fusion [48, 49]	GLI1-altered soft-tissue tumour
16	Poorly differentiated carcinoma of unknown primary vs undifferentiated sarcoma	Truncating *NF2* mutation + haploidisation [12]	Peritoneal mesothelioma
17	High-grade bone sarcoma with suspected BCOR alteration (by IHC)	*TP53* exon 1 truncating mutation [13] + amplifications in 4q/*MYOCD/RICTOR/COPS3* [50] Wild-type *BCOR* locus	Osteosarcoma
18	Metastatic sex cord-stromal tumour vs endometrial stromal sarcoma	*JAZF1::SUZ12*	Low-grade endometrial stromal sarcoma
24	Hamartomatous vascular malformation	*PIK3CA* mutation [51]	PIK3CA mutated vascular neoplasm

nature COMMUNICATIONS

2022

Memorial Sloan Kettering Cancer Center, **New York, NY, USA**.

ARTICLE

https://doi.org/10.1038/s41467-022-30496-0 OPEN

Clinical genomic profiling in the management of patients with soft tissue and bone sarcoma

Mrinal M. Gounder[1,2✉], Narasimhan P. Agaram[1], Sally E. Trabucco[3], Victoria Robinson[1], Richard A. Ferraro[1,2], Sherri Z. Millis[3], Anita Krishnan[1], Jessica Lee[3], Steven Attia[4], Wassim Abida[1,2],

- Patients' median age was 53 years (range <1–89 years) and 53.4% were female. Pediatric, adolescent, and young adult (P-AYA) patients, defined as age ≤30 years, constituted 21.8% (1636/7494) of the cohort.
- Tumor tissue (without normal tissue) was profiled by massively parallel, next-generation sequencing (NGS) of 465 genes, select introns of 31 genes involved in rearrangements, and RNA sequencing (cDNA) of 333 commonly rearranged genes to better identify de novo and rare gene fusions using the FoundationOne HEME™ platform

- Through targeted panel sequencing of 7494 sarcomas representing 44 histologies, we identify highly recurrent and type-specific alterations that aid in diagnosis and treatment decisions.
- Sequencing could lead to refinement or reassignment of 10.5% of diagnoses.
- Nearly one-third of patients (31.7%) harbor potentially actionable alterations, including a significant proportion (2.6%) with kinase gene rearrangements; 3.9% have a tumor mutational burden ≥10 mut/Mb.
- In a clinically annotated subset of 118 patients, we validate actionable genetic events as therapeutic targets.
- Collectively, our findings reveal the genetic landscape of human sarcomas, which may inform future development of therapeutics and improve clinical outcomes for patients with these rare cancers.
- Genomic sequencing may allow avoidance of harmful or non-beneficial therapies

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2025

Soft Tissue Sarcoma

Genetic predisposition in sarcomas: clinical implications and management

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Genetic tests and genetic syndromes

Certain genetic syndromes increase the risk of developing soft tissue sarcoma. Changes in different genes (called mutations) cause each of these genetic syndromes.

You inherit your genes from your parents. In hereditary or genetic syndromes, your siblings, your parents' siblings, and your grandparents often have the same mutation.

Testing for gene mutations that cause these syndromes may help treat soft tissue sarcoma and monitor you or your family members for cancers.

Share what you know about your personal health and family history with your care team. If your health care provider thinks you may have a genetic syndrome that is causing your cancer, you may benefit from genetic testing.

Testing should be carried out by a pathologist who's experienced in genetic testing techniques. A genetic counselor may speak with you about the results. A genetic counselor is an expert who has special training in genetic diseases.

Syndrome/condition	Gene	Disease inheritance	Sarcomas
Li-Fraumeni	*TP53*	AD	Bone and soft tissue sarcomas - osteosarcoma most frequently associated.
Retinoblastoma	*RB1*	AD	Bone and soft tissue sarcomas - LMS most frequently associated.
Familial adenomatous polyposis (FAP)	*APC*	AD/sporadic	Desmoid tumours
Neurofibromatosis type1 (a 'RASopathy')	*NF1*	AD	MPNST RMS GIST
GIST: Carney Stratakis	*SDHA, SDHB, SDHC, SDHD*	AD	GIST (multifocal)
GIST predisposition	*KIT*	AD	GIST (multifocal)
GIST predisposition	*PDGFRA*	AD	GIST (multifocal)
Tuberous sclerosis	*TSC1, TSC2*	AD	PEComa Chordoma
POT1 tumour predisposition	*POT1*	AD	Angiosarcoma Other bone and soft tissue sarcomas reported
Paget disease of bone	*TNFRSF11A, TNFRSF11B, SQSTM1, PDB4, ZNF687*	AD/unclear	Osteosarcoma Chondrosarcoma Fibrosarcoma
Mazabraud	*GNAS1*	Sporadic	Bone sarcomas including osteosarcoma, chondrosarcoma
McCune Albright	*GNAS1*	Sporadic	Osteosarcoma
Werner	*RECQL2*	AR	Osteosarcoma
Bloom	*RECQL3*	AR	Osteosarcoma RMS
Rothmund-Thomson and RAPADILINO	*RECQL4*	AR	Osteosarcoma
Multiple hereditary exostoses (multiple osteochondromas)	*EXT1, EXT2*	AD	Chondrosarcoma
Endochondromatosis: Maffucci	*IDH1, IDH2*	Embryonic mosaicism	Chondrosarcoma Osteosarcoma Fibrosarcoma Vascular sarcomas
Endochondromatosis: Ollier disease	*IDH1, IDH2*	Embryonic mosaicism	Chondrosarcoma
Beckwith-Wiedemann	(epi)genetic 11p15 alteration	Embryonic mosaicism/AD	RMS
Constitutional mismatch repair	*PMS2, MLH1, MSH2, MSH6*	AR	RMS
Basal cell nevus (Gorlin-Goltz)	*PTCH1, PTCH2, SUFU*	AD	RMS LMS
Nijmegen breakage	*NBN*	AR	RMS
DICER1	*DICER1*	AD	RMS Gynaecological adenosarcoma
Costello (a 'RASopathy')	*HRAS*	AD	RMS

Syndrome/condition	Gene	Disease inheritance	Sarcomas
(Continued from previous page)			
Noonan (a 'RASopathy')	Multiple genes including *PTPN11* (50%), *SOS1*, *CREBBP*, *RAF*, *RIT1*, *KRAS* and others	AD	RMS Angiosarcoma
Multilineage mosaic RASopathies	*HRAS*, *KRAS*	Embryonic mosaicism	RMS (urogenital)
Mosaic variegated aneuploidy	*BUB1B*, *CEP57*, *TRIP13*	AR	RMS
Familial rhabdoid predisposition	*SMARCB1/INI1*	AD	Malignant rhabdoid tumour
Hereditary leiomyomatosis and renal cell cancer	*FH*	AD	LMS (Uterine)
BRCA related cancer predisposition	*BRCA1*, *BRCA2*	AD	To be defined - bone and soft tissue sarcomas
Lynch	*MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*	AD	Bone and soft tissue sarcomas - pleomorphic soft tissue sarcomas most frequent

- Recent studies indicate up to 20% of sarcomas may be associated with predisposition genes, and this number will probably increase as genetic testing becomes more available.
- Evidence on the management of patients with sarcoma and genetic predisposition remains, however, scarce.
- Genetic predisposition may influence treatment decisions and clinical management, focusing on surgery, radiotherapy, systemic treatment, and surveillance.
- Evidence-based recommendations are currently not available for most syndromes, and we have therefore included pragmatic advice for clinicians.

The epigenomics of sarcoma

- Epigenetic mechanisms of tumorigenesis have been implicated in mesenchymal tumors
  - ranging from chondroblastoma and giant cell tumor of bone to chondrosarcoma, malignant peripheral nerve sheath tumor, synovial sarcoma, epithelioid sarcoma and Ewing sarcoma: aggressive diseases which present in a younger patient population than most cancers.
- Targeted sequencing approaches focusing on proliferation and apoptosis-related "cancer genes" in sarcomas (and gliomas) failed to include many genes involved in epigenetic control and thus, for instance, *IDH1* mutations were therefore instead first identified by a whole exome approach in gliomas.
- Thus, further clinical progress in targeting epigenetic dysregulation in sarcomas will depend on expanded clinical genomic testing that includes genes involved in epigenetic pathways as well as robust profiling of DNA methylation and histone modifications carefully paired with new agents that can specifically target these aberrant epigenetic states.

PMID: 32782366

Conclusion

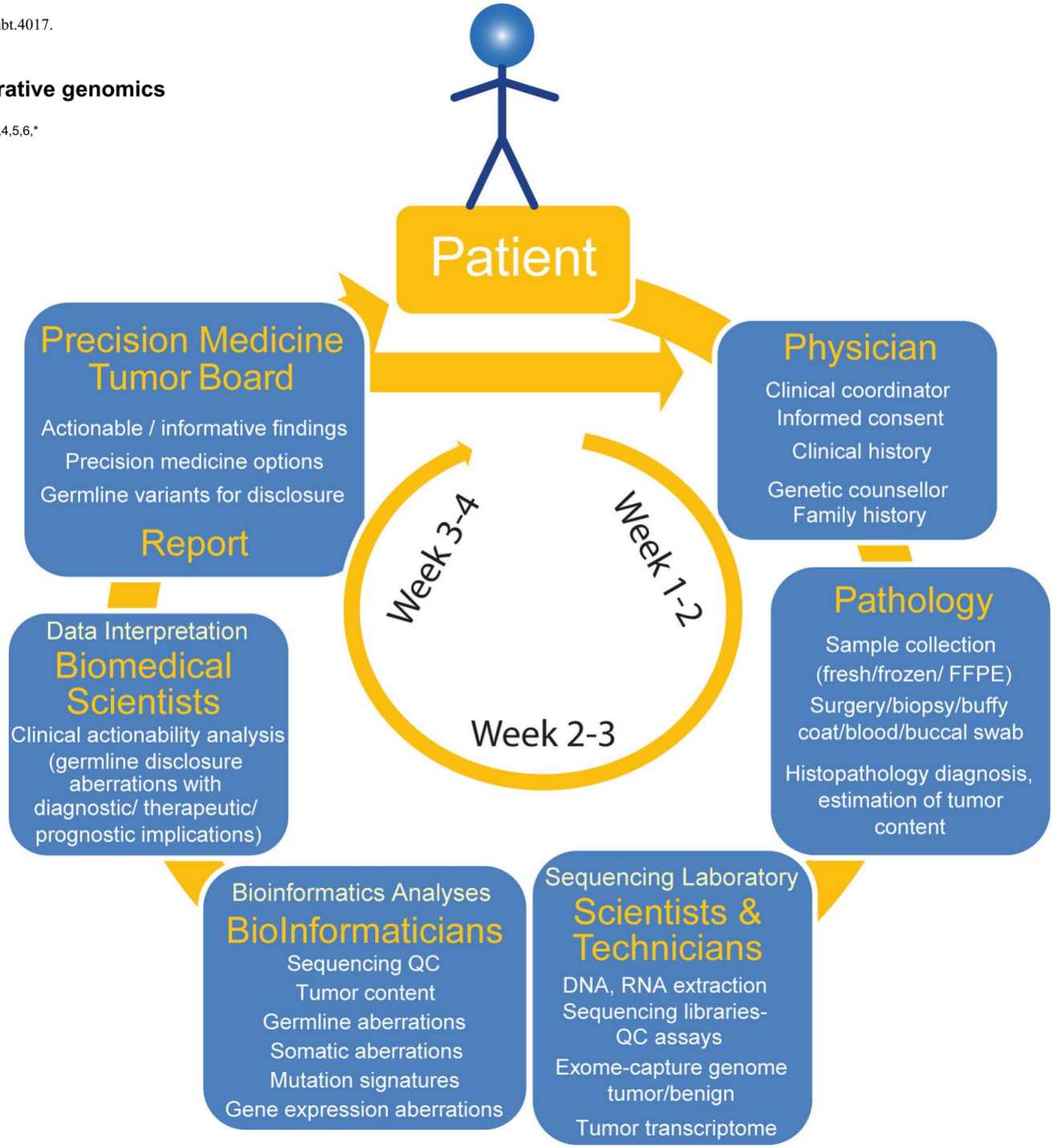
- Precision Oncology
- Genomics vs Epigenomics
- Genomic Profile vs Genetic Profile
- Integrated Genomics/ICS/IGS
- Somatic vs Germline
- STS vs Bone Sarcoma
- Pediatrics vs Adult
- Treatment vs Diagnosis & Prognosis
- Guidelines

Thanks for Attention

Nat Biotechnol. 2018 January 10; 36(1): 46–60. doi:10.1038/nbt.4017.

Precision oncology in the age of integrative genomics

Chandan Kumar-Sinha[1,2,*] and **Arul M. Chinnaiyan**[1,2,3,4,5,6,*]
[1]Michigan Center for Translational Pathology



Nat Biotechnol. 2018 January 10; 36(1): 46–60. doi:10.1038/nbt.4017.

Precision oncology in the age of integrative genomics

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Year	Landmarks in the application of analytical tools to inform cancer diagnosis, prognosis, and therapy*
1847	**Microscopy** Formal description of "Leukemia" by Rudolf Virchow[1,2]
1941	**Cytopathology** Hematoxylin and Eosin (H&E) staining of Papanicolaou-smear, cervical cancer[3,4]
1956	*Improved karyotyping: accurate determination of human chromosome numbers*[5,6]
1960s	**Cytogenetics** Philadelphia chromosome, chronic myeloid leukemia (CML)[7]
	Electron microscopy Epstein Barr Virus (EBV) associated with Burkitt's lymphoma[8]
1970s	**Chromosome banding** Recurrent translocations in hematological malignancies[9-15]
	Radioimmunoassay Carcinoembryogenic antigen (CEA), colorectal cancer[16,17]
	DNA sequencing[18-20]*, molecular cloning*[21]
1980s	**Chromosome banding** Recurrent translocations in sarcomas/ soft tissue tumors[22-25]
	Radioactive probe hybridizations Detection of BCR-ABL1, CML[26]; IgH-BCL2, B-Cell lymphoma[27]; TcR-MYC, T-cell leukemia[28]; human papilloma virus (HPV) in cervical cancer[29] **Fluorescence in situ hybridization (FISH)**[30,31] ERBB2 in breast cancer[32]
	Flow cytometry Acute promyelocytic leukemia (APML)[33], neuroblastoma[34], myelodysplastic syndrome (MDS)[35], multiple myeloma[36]
	Oncogenes and tumor suppressors: identification and characterization eg. RAS, MYC, RB1[37-39]
	Radioimmunoassay Estrogen receptor[40], prostate specific antigen[41]
	Immunohistochemistry Estrogen receptor[40,42], ERBB2[43,44]
	Invention of PCR[45]
	Reverse transcriptase PCR (RT-PCR) BCR-ABL1 in CML[46], PML-RARA in APML[47], AML1/ETO in AML (acute myeloid leukemia)[48]
1990s	*Human Genome Project*[49,50]
	Positron emission tomography (PET), computed tomography (CT)[51-53]
	Microarray profiling for high-throughput genomic and transcriptomic profiling of cancers[54] Expression profiles of cancers[55,56], diffuse large B-cell lymphoma (DLBCL) subtypes[57], breast cancer prognosis[58], hereditary breast cancer[59], biomarkers of prostate cancer[60], lung cancer[61], gene fusions in prostate cancer[62]
2000s	**PCR amplification and sequencing of "cancer genes"**[63] **from tumor specimens** Genomic landscapes of somatic aberrations in different cancers- breast, colorectal, pancreatic[64-67]
	Massively parallel high-throughput/ next-generation sequencing[68-70]
	TCGA- The Cancer Genome Atlas[71-75], https://cancergenome.nih.gov/
	Various modalities of precision oncology projects in research, clinical, and clinical trial settings discussed in this review
	Precision Medicine Initiative[76-78] Cancer Breakthroughs 2020 (formerly, Cancer Moonshot), http://www.cancerbreakthroughs2020.org/

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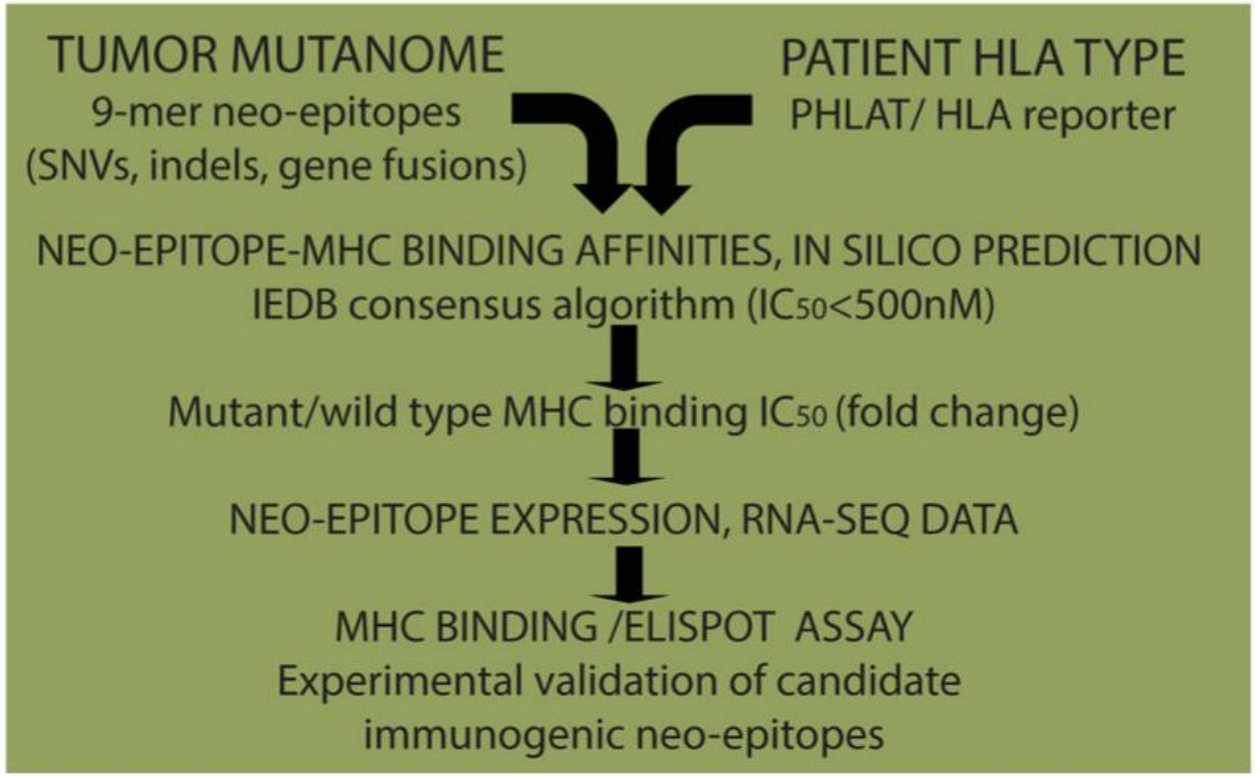
Prediction and validation of neo-antigens for immunotherapy



Article | Published: 05 October 2020

Whole genome, transcriptome and methylome profiling enhances actionable target discovery in high-risk pediatric cancer

Marie Wong, Chelsea Mayoh, Loretta M. S. Lau, Dong-Anh Khuong-Quang, Mark Pinese, Amit Kumar, Paulette Barahona, Emilie E. Wilkie, Patricia Sullivan, Rachel Bowen-James, Mustafa Syed, Iñigo Martincorena, Federico Abascal, Alexandra Sherstyuk, Noemi A. Bolanos, Jonathan Baber, Peter Priestley, M. Emmy M. Dolman, Emmy D. G. Fleuren, Marie-Emilie Gauthier, Emily V. A. Mould, Velimir Gayevskiy, Andrew J. Gifford, Dylan Grebert-Wade, ... Mark J. Cowley + Show authors

Nature Medicine **26**, 1742–1753 (2020) | Cite this article

Children's Cancer Institute, Lowy Cancer Centre, UNSW Sydney, Kensington, NSW, **Australia**.

The Zero Childhood Cancer Program

- **Using tumor and germline WGS and RNAseq across 252 tumors from high-risk pediatric patients with cancer**
- Identified 968 reportable molecular aberrations
  - (39.9% in WGS and RNAseq, 35.1% in WGS only and 25.0% in RNAseq only).
  - Of these patients, 93.7% had at least one germline or somatic aberration, 71.4% had therapeutic targets and 5.2% had a change in diagnosis.
- WGS identified pathogenic cancer-predisposing variants in 16.2% of patients.
- In 76 **CNS tumors, methylome analysis** confirmed diagnosis in 71.1% of patients and contributed to a change of diagnosis in two patients (2.6%).
- To date, 43 patients have received a recommended therapy, 38 of whom could be evaluated, with 31% showing objective evidence of clinical benefit.
- Comprehensive molecular profiling **resolved the molecular basis of virtually all high-risk cancers, leading to clinical benefit in some patients**.