9e ÉDITION

JOURNÉES DU **GFCO 2023**

Biomarqueurs et analyses moléculaires en oncologie

Avec la participation scientifique du GFCO

MÉTHYLOME : techniques et applications présentes et futures

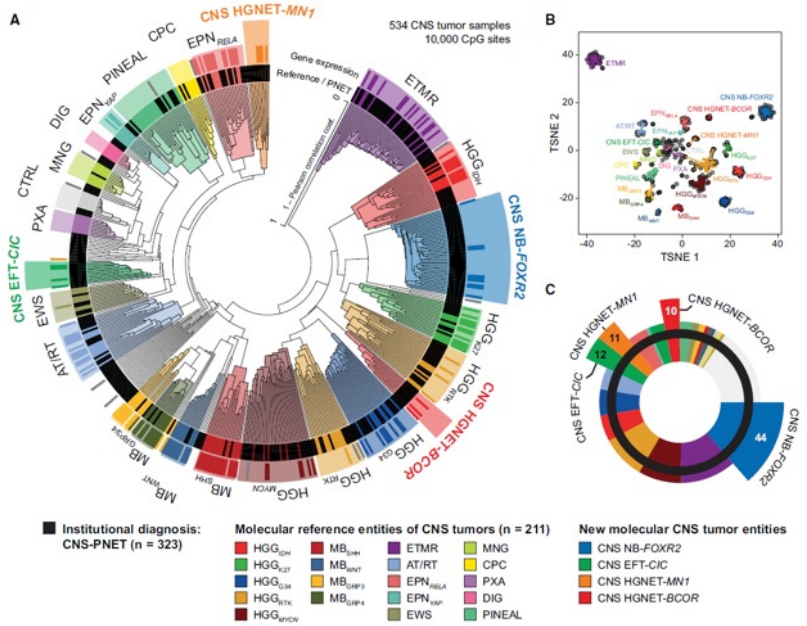
Pr Pascale VARLET, GHU-Paris Sainte-Anne

LIENS D'INTÉRÊT

- **Aucun, en particulier Illumina**

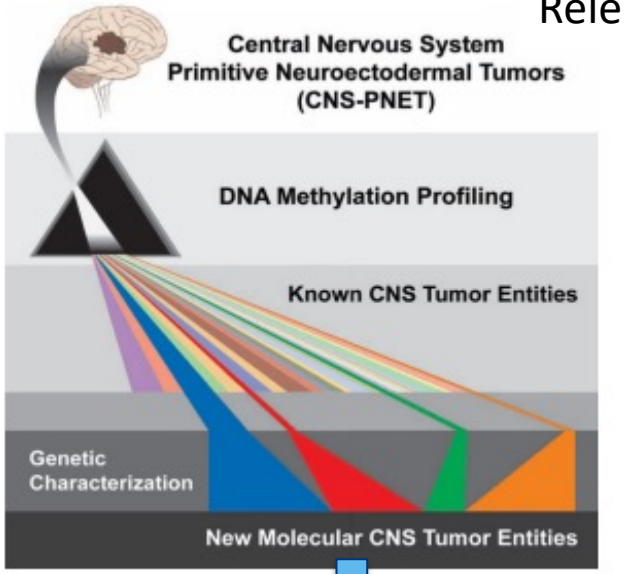
Méthylome et neuro-oncologie pédiatrique

dkfz. | UniversitätsKlinikum Heidelberg | KiTZ Hopp-Kindertumorzentrum Heidelberg | MolecularNeuropathology.org



Sturm D *et al.* Cell. 2016

Relecture centrale

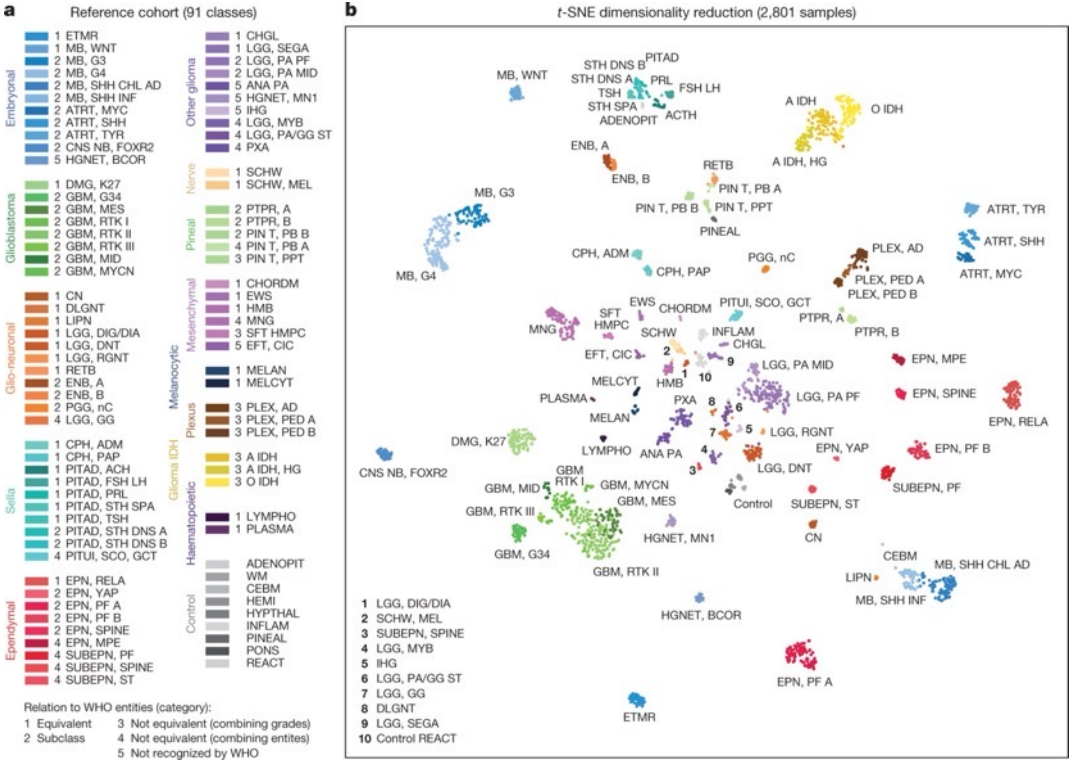


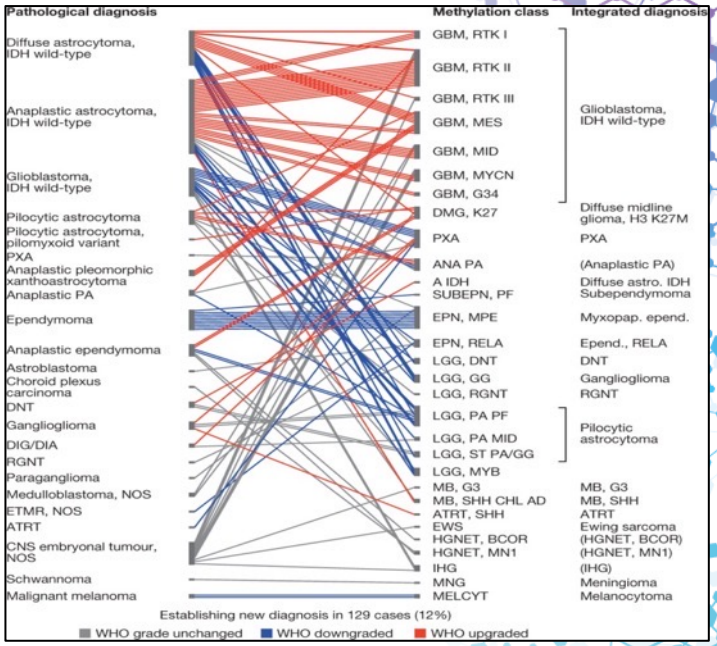
GHU PARIS PSYCHIATRIE & NEUROSCIENCES Neuro Sainte-Anne

International Agency for Research on Cancer
World Health Organization
2021

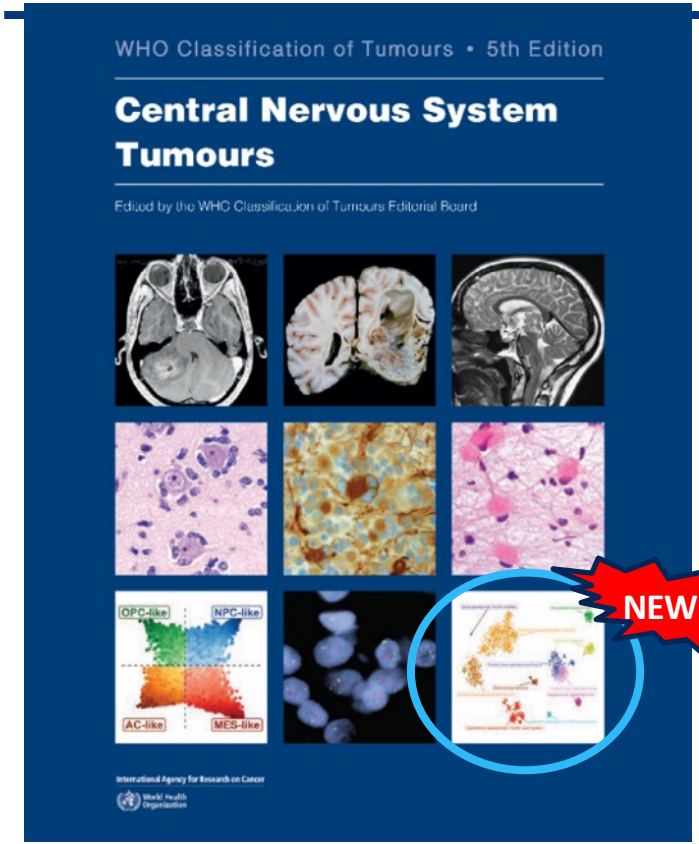
Méthylome et neuro-oncologie pédiatrique

Capper D *et al. Nature* 555, 469–474 (2018)





Officialisation de la place du méthylome dans le diagnostic des tumeurs cérébrales dans la classification de l'OMS 2021



International Agency for Research on Cancer
World Health Organization

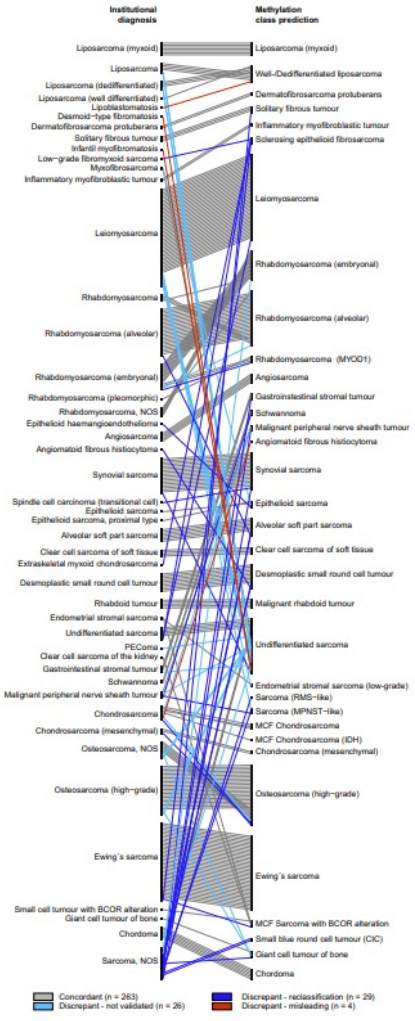
45 types tumoraux comportent le profil de méthylation de l'ADN en tant que critères diagnostiques essentiels ou désirables

International Agency for Research on Cancer
World Health Organization

Critères diagnostiques des astrocytomes de haut-grade avec aspect piloïde (HGAP)

NEW

Essential:
An astrocytic glioma
AND
A DNA methylation profile of high-grade astrocytoma with piloid features
Desirable:
MAPK pathway gene alteration
Homozygous deletion or mutation of *CDKN2A* and/or *CDKN2B*, or amplification of *CDK4*
Mutation of *ATRX* or loss of nuclear ATRX expression
Anaplastic histological features

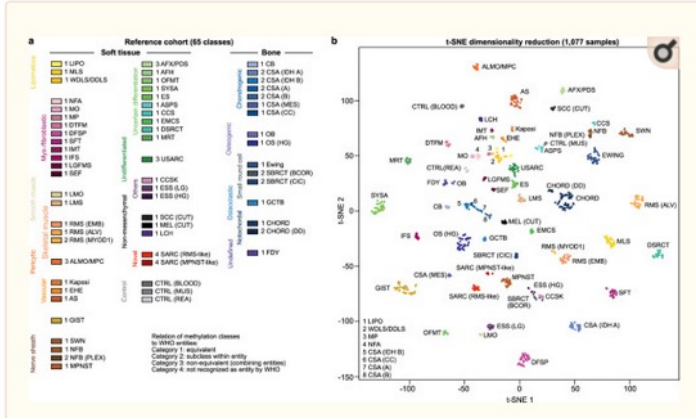


nature COMMUNICATIONS

ARTICLE

https://doi.org/10.1038/s41467-020-20603-4 OPEN

Sarcoma classification by DNA methylation profiling



The Journal of Pathology: Clinical Research
J Pathol Clin Res July 2021; 7: 350–360
Published online 5 May 2021 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/cjp2.215

ORIGINAL ARTICLE

DNA methylation-based profiling of bone and soft tissue tumours: a validation study of the 'DKFZ Sarcoma Classifier'

Iben Lyskjær[1,2†], Solange De Noon[1,3†], Roberto Tirabosco[3], Ana Maia Rocha[1,3], Daniel Lindsay[1,3], Fernanda Amary[1,3], Hongtao Ye[3], Daniel Schrimpf[4,5], Damian Stichel[5], Martin Sill[6,7], Christian Koelsche[4,5,8], Nischalan Pillay[1], Andreas Von Deimling[4,5], Stephan Beck[2] and Adrienne M Flanagan[1,3*]

Multicenter Study > J Cancer Res Clin Oncol. 2020 Jan;146(1):97-104.
doi: 10.1007/s00432-019-03093-w. Epub 2019 Nov 25.

DNA methylation-based profiling of uterine neoplasms: a novel tool to improve gynecologic cancer diagnostics

Felix K F Kommoss [1], Damian Stichel [2 3], Daniel Schrimpf [2 3], Mark Kriegsmann [1], Basile Tessier-Cloutier [4], Aline Talhouk [4], Jessica N McAlpine [5], Kenneth T E Chang [6], Dominik Sturm [7 8 9], Stefan M Pfister [7 8 9], Laura Romero-Pérez [10], Thomas Kirchner [11], Thomas G P Grünewald [10], Rolf Buslei [12], Hans-Peter Sinn [1], Gunhild Mechtersheimer [1], Peter Schirmacher [1], Dietmar Schmidt [13], Hans-Anton Lehr [14], Felix Sahm [2], David G Huntsman [4], C Blake Gilks [4], Friedrich Kommoss [14], Andreas von Deimling [2 3], Christian Koelsche [15]

nature communications

Article

https://doi.org/10.1038/s41467-022-34815-3

DNA methylation-based classification of sinonasal tumors

Received: 31 March 2022

Accepted: 7 November 2022

Published online: 28 November 2022

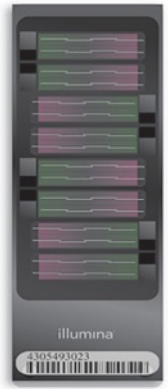
Check for updates

A list of authors and their affiliations appears at the end of the paper

The diagnosis of sinonasal tumors is challenging due to a heterogeneous spectrum of various differential diagnoses as well as poorly defined, disputed entities such as sinonasal undifferentiated carcinomas (SNUCs). In this study, we apply a machine learning algorithm based on DNA methylation patterns to classify sinonasal tumors with clinical-grade reliability. We further show that sinonasal tumors with SNUC morphology are not as undifferentiated as their current terminology suggests but rather reassigned to four distinct molecular classes defined by epigenetic, mutational and proteomic profiles. This includes two classes with neuroendocrine differentiation, characterized by *IDH2* or *SMARCA4/ARID1A* mutations with an overall favorable clinical course, one class composed of highly aggressive SMARCB1-deficient carcinomas and another class with tumors that represent potentially previously misclassified adenoid cystic carcinomas. Our findings can aid in improving the diagnostic classification of sinonasal tumors and could help to change the current perception of SNUCs.

Principes de la technique de méthylome

Séquençage pan-génomique de 850.000 ilots CpG répartis sur le génome



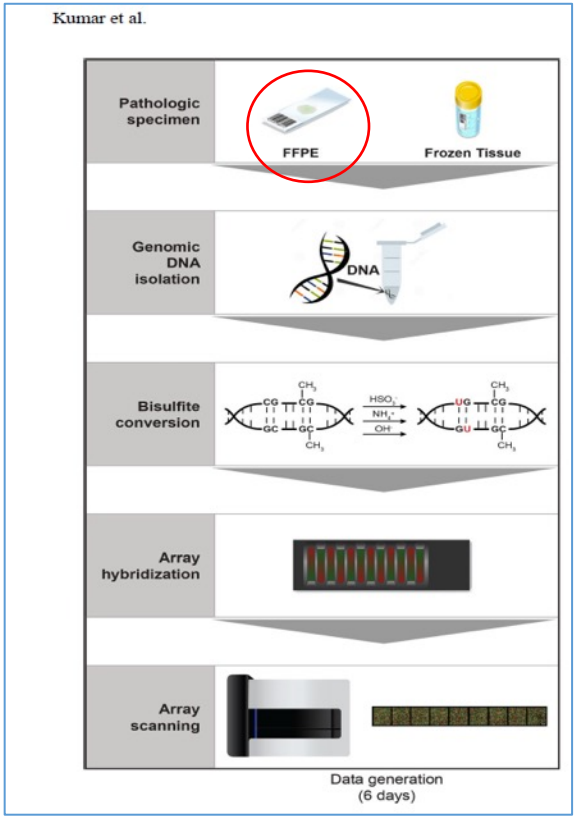
Analyses bio-informatiques couplées à des outils d'intelligence artificielle via algorithme gratuit

www.molecularneuropathology.org.

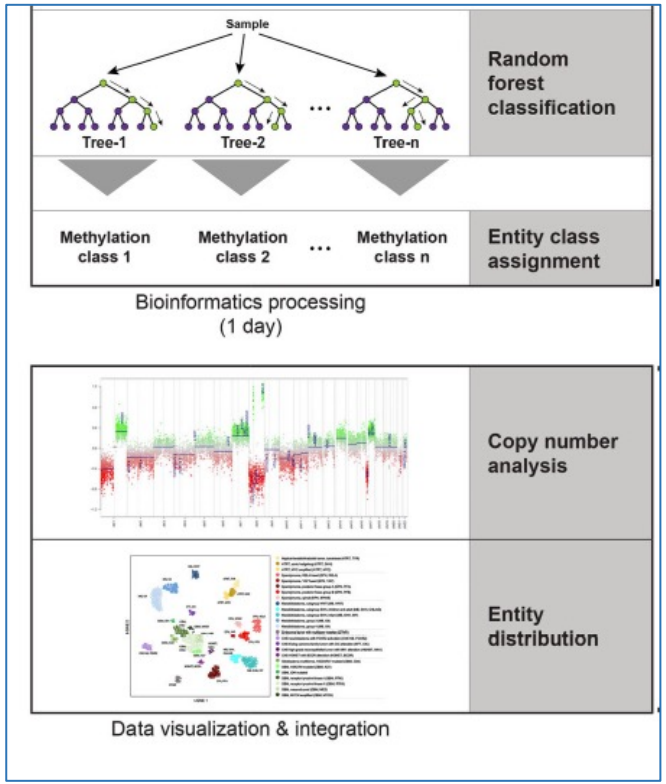
dkfz. UniversitätsKlinikum Heidelberg KiTZ Hopp-Kindertumorzentrum am NCT Heidelberg MolecularNeuropathology.org

Sturm *et al.,* Cell 2016; Capper *et al.,* Nature 2018

Principes de la technique de méthylome



.idat files



.idat files

SCORE

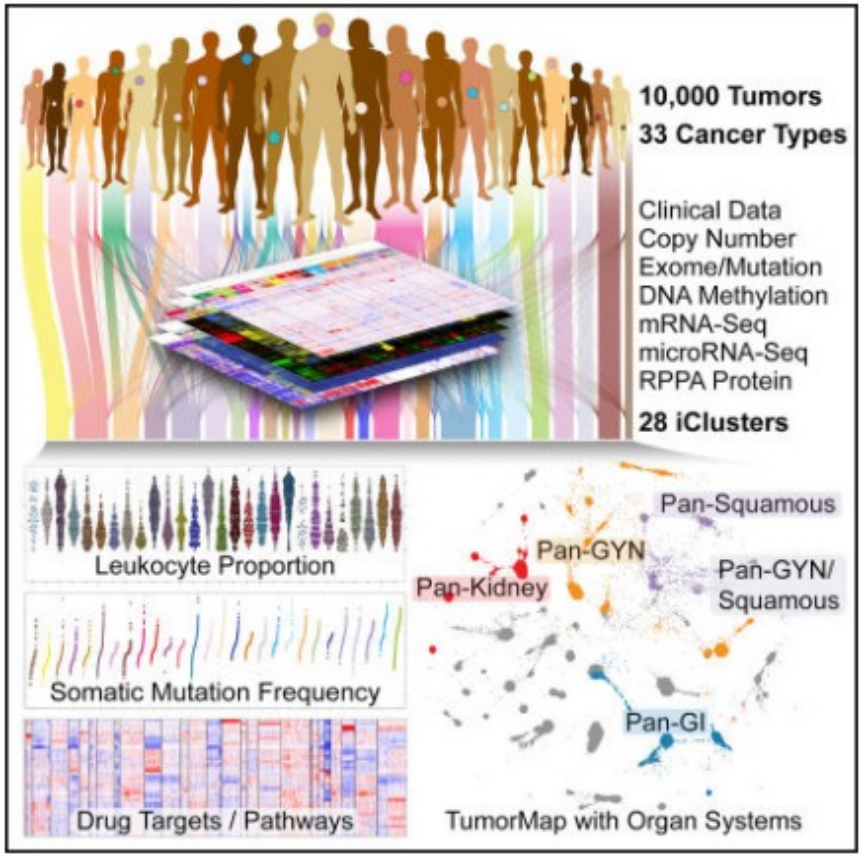
reflète
- Origine cellulaire
- Oncogenèse Intrinsèque
- CNV

Kumar et al. Cancer, 2018. 124: 4168-4180.

Published in final edited form as:
Cell. 2018 April 05; 173(2): 291–304.e6. doi:10.1016/j.cell.2018.03.022.

Cell-of-Origin Patterns Dominate the Molecular Classification of 10,000 Tumors from 33 Types of Cancer

Katherine A. Hoadley[1,21,*], **Christina Yau**[2,3,21], **Toshinori Hinoue**[4,21], **Denise M. Wolf**[5,21], **Alexander J. Lazar**[6,21], **Esther Drill**[7,21], **Ronglai Shen**[7,21], **Alison M. Taylor**[8,9,21], **Andrew D. Cherniack**[8,9,21], **Vésteinn Thorsson**[10,21], **Rehan Akbani**[6,21], **Reanne Bowlby**[11,21], **Christopher K. Wong**[12,21], **Maciej Wiznerowicz**[13,14,15], **Francisco Sanchez-Vega**[16], **A. Gordon Robertson**[11], **Barbara G. Schneider**[17], **Michael S. Lawrence**[8,18], **Houtan Noushmehr**[19,20], **Tathiane M. Malta**[19,20], **The Cancer Genome Atlas Network**, **Joshua M. Stuart**[12], **Christopher C. Benz**[2], and **Peter W. Laird**[4,22,*]



dkfz. | UniversitätsKlinikum Heidelberg | KiTZ Hopp-Kindertumorzentrum am NCT Heidelberg | MolecularNeuropathology.org

Home | Classifier | Reference set | Upload sample | Analysis | Contact | Legal notice | Data privacy | en | Sign in | Registration

Welcome to MolecularNeuropathology.org - The platform for next generation neuropathology.

This website represents the access point for DNA methylation-based classification of central nervous system tumors. For the scientific background and interpretation of the data, please see Capper D, Jones DTW, Sill M, Hovestadt V et al., Nature. 2018 Mar 22;555(7697):469-474.

To implement the methylation profiling classifier you are required to generate and upload unprocessed IDAT-files of Illumina Human Methylation 450 BeadChip arrays or EPIC BeadChip arrays of your samples of interest. This data is then automatically compared to methylation data of a reference cohort comprising over 2800 neuropathological tumors of almost all known entities (currently over 80 tumor classes or subclasses included). Within a short time you will receive an E-Mail report of the methylation profiling of your case, a low resolution copy number plot calculated from your array data (useful e.g. for 1p/19q analysis or the detection of all sorts of amplifications and deletions) and an estimation of MGMT promoter methylation status.

Occasional updates may be required for either inclusion of new tumor classes or subtle changes of the EPIC array probe composition that may occur in a new batch. Older version will remain available.

Classification using methylation profiling is a research tool under development, it is not verified and has not been clinically validated. Implementation of the results in a clinical setting is in the sole responsibility of the treating physician.

Upload statistics:

IDAT files processed:	58132
Samples approved for classifier development:	43749
Statistics updated:	2020-12-28 15:39 UTC

Cohorte de référence: 2800 tumeurs

Répartis en 82 classes tumorales (MC)
en 9 classes non tumorales

Classifier list

Created At	Name	Version	Details
2016-10-11T10:32:18.000000Z	11b2	11b2	show
2017-10-06T09:25:31.000000Z	11b4	11b4	show
2018-03-24T15:45:44.000000Z	sarcoma classifier	8.0	show
2018-03-24T15:45:44.000000Z	meningioma classifier	2.0	show
2018-11-20T09:28:23.000000Z	meningioma classifier	2.4	show
2018-11-20T09:28:23.000000Z	sarcoma classifier	10.0	show
2018-11-20T09:28:23.000000Z	medulloblastoma classifier group 3/4	1.0	show
2019-08-11T15:04:10.000000Z	sarcoma classifier	10.1	show
2019-11-26T08:30:30.000000Z	sarcoma classifier	12.2	show
2021-08-15T09:30:03.000000Z	brain classifier	12.3	show

V 11

V 12.3

Methylation profiling report

dkfz. GERMAN CANCER RESEARCH CENTER IN THE HELMHOLTZ ASSOCIATION

Heidelberg University Hospital

Molecular Neuropathology 2.0

Supplier information

		Automatic prediction		
Sample identifier:	Sample 1			
Sentrix ID:	3999079060_R05C02	Array type:	450k	
Material type:	FFPE DNA	Material type:	FFPE DNA	✓
Gender:	male	Gender:	male	✓
Supplier diagnosis:	Glioblastoma (WHO grade IV)	Legend: ✓ OK ! Supplier information or prediction not available		✗ Warning, missmatch of prediction and supplier information

Brain tumor methylation classifier results (v11b2)

Methylation classes (MCs with score >= 0.3)	Calibrated score	Interpretation	
methylation class family Glioblastoma, IDH wildtype	0.99	match	✓
MC family members with score >= 0.1			
methylation class glioblastoma, IDH wildtype, subtype RTK II	0.78	match	●
methylation class glioblastoma, IDH wildtype, subtype RTK I	0.18		

Legend: ✓ Match (score >= 0.9) ✗ No match (score < 0.9); possibly still relevant for low tumor content and low DNA quality cases. ● Match to MC family member (score >= 0.5)

Class descriptions

Methylation class family Glioblastoma, IDH wildtype: The methylation class family "Glioblastoma, IDH wildtype" comprises the methylation classes glioblastoma, IDH wildtype, subtype RTK I to III, glioblastoma, IDH wildtype, subtype mesenchymal, glioblastoma, IDH wildtype, subtype MYCN and glioblastoma, IDH wildtype, subtype midline.

Methylation class glioblastoma, IDH wildtype, subtype RTK II: The methylation class "glioblastoma, IDH wildtype, subtype RTK II" is comprised of tumors with a histological diagnosis of glioblastoma, IDH wildtype and rarely gliosarcoma, IDH wildtype. These tumors are typically located in the cerebral hemispheres. Median age is 61 years (range 35 to 85). Recurrent chromosomal alterations are gain of chromosome 7 with or without EGFR amplification (>80%), loss of 9p21 (CDKN2A/B; >70%) and chromosome 10 loss (>90%). Gain of chromosome 19 and 20 is also recurrently observed (40% of cases). Expression profiles often resemble the "Classical" subgroup according to the TCGA classification.

Methylation class glioblastoma, IDH wildtype, subtype RTK I: The methylation class "glioblastoma, IDH wildtype, subtype RTK I" is comprised of tumors with a histological diagnosis of glioblastoma, IDH wildtype. The tumors are located in the cerebral hemispheres. Median age is 64 years (range 29 to 84). Recurrent chromosomal alterations are gain of chromosome 7 with or without EGFR amplification (>80%), loss of 9p21 (CDKN2A/B; >70%) and chromosome 10 loss (>70%). Amplifications of the PDGFRA oncogene are enriched in this class (present in 20-30% of cases). Expression profiles often resemble the "Proneural" subgroup according to the TCGA classification.

Copy number variation profile

Depiction of chromosome 1 to 22 (and X/Y if automatic prediction was successful). Gains/amplifications represent positive, losses negative deviations from the baseline. 25 brain tumor relevant gene regions are highlighted for easier assessment.
(see Hovestadt & Zapatka, http://www.bioconductor.org/packages/devel/bioc/html/conumee.html)

MGMT promotor methylation (MGMT-STP27)

MGMT promotor status prediction

0.00 0.25 0.50 0.75 1.00
Score (red line cutoff=0.3562)

Status	Estimated	CI lower	CI upper
not determinable	0.18186	0.05665	0.43795

(see Bady et al, J Mol Diagn 2016; 18(3):350-61)

Disclaimer

Classification using methylation profiling is a research tool under development, is not verified and has not been clinically validated. Implementation of the results in a clinical setting is in the sole responsibility of the treating physician.
Intended for non-commercial use only.

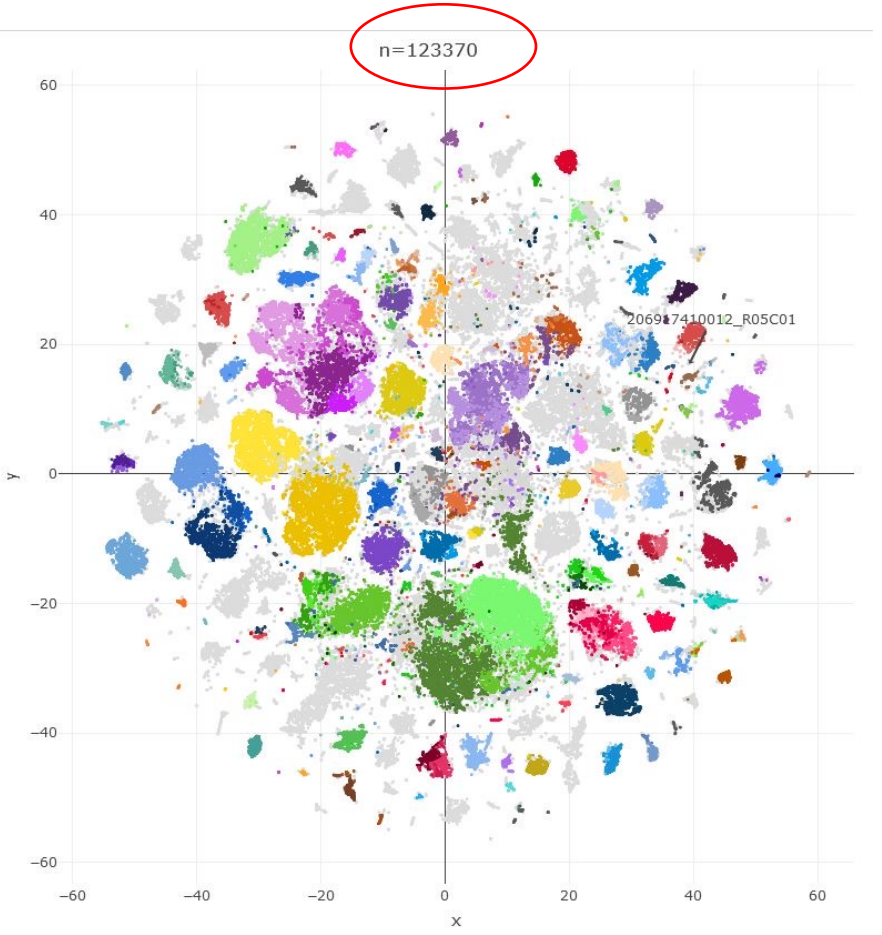
Information échantillon anonymisé

SCORE INFORMATIF si > 0,9

Profil de variation nombre de copies (CNV)

Profil de méthylation MGMT

Fév. 2023



dkfz.

UniversitätsKlinikum Heidelberg

KiTZ
Hopp-Kindertumorzentrum
Heidelberg

MolecularNeuropathology.org

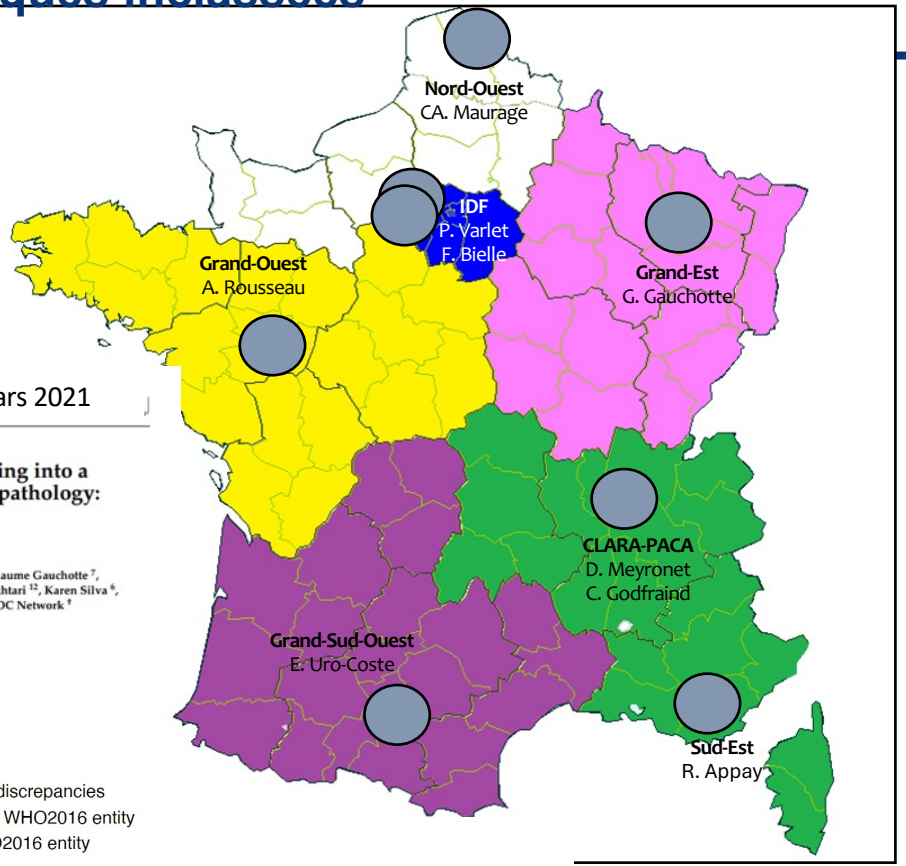
Auffret L *et al*, 2023
Acta Neuropathologica, in press

GHU PARIS PSYCHIATRIE & NEUROSCIENCES Neuro Sainte-Anne

GUSTAVE ROUSSY CANCER CAMPUS GRAND PARIS

Étude nationale 2018-2020: Technique de méthylome pour toutes les tumeurs pédiatriques inclassées

RÉseau de Neuro-Oncologie CLInico-Pathologique



Technique du méthylome disponible dans chaque inter-région en 2022-2023

RÉseau de Neuro-Oncologie CLInico-Pathologique

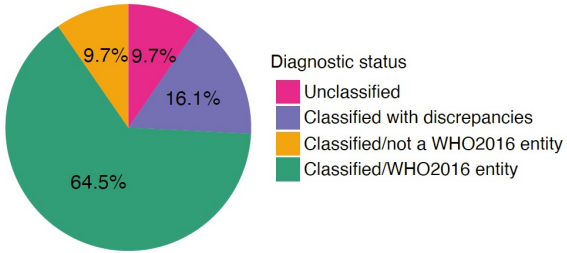
cancers

Mars 2021

Article

The Implementation of DNA Methylation Profiling into a Multistep Diagnostic Process in Pediatric Neuropathology: A 2-Year Real-World Experience by the French Neuropathology Network

Melanie Pages [1,*], Emmanuelle Uro-Coste [2,3,4], Carole Colin [5], David Meyronet [6], Guillaume Gauchotte [7], Claude-Alain Maurage [8], Audrey Rousseau [9,10], Catherine Godfraind [11], Karima Mokhtari [12], Karen Silva [6], Dominique Figarella-Branger [5,13], Pascale Varlet [1,*] and on behalf of the RENOCLIP-LOC Network †



Intérêts

Published in final edited form as:
Cell. 2018 April 05; 173(2): 291–304.e6. doi:10.1016/j.cell.2018.03.022.

Cell-of-Origin Patterns Dominate the Molecular Classification of 10,000 Tumors from 33 Types of Cancer

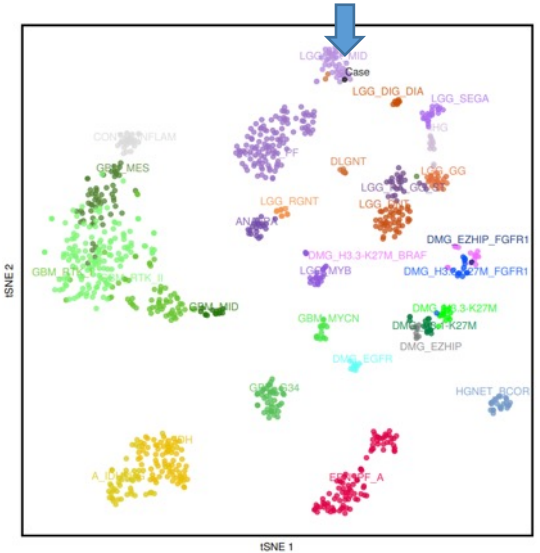
Katherine A. Hoadley[1,21,*], Christina Yau[2,3,21], Toshinori Hinoue[4,21], Denise M. Wolf[5,21], Alexander J. Lazar[6,21], Esther Drill[7,21], Ronglai Shen[7,21], Alison M. Taylor[8,9,21], Andrew D. Cherniack[8,9,21], Vésteinn Thorsson[10,21], Rehan Akbani[6,21], Reanne Bowlby[11,21], Christopher K. Wong[12,21], Maciej Wiznerowicz[13,14,15], Francisco Sanchez-Vega[16], A. Gordon Robertson[11], Barbara G. Schneider[17], Michael S. Lawrence[8,18], Houtan Noushmehr[19,20], Tathiane M. Malta[19,20], The Cancer Genome Atlas Network, Joshua M. Stuart[12], Christopher C. Benz[2], and Peter W. Laird[4,22,*]

- **Technique robuste (FFPE) nécessitant < 200 ng d'ADN**
- **Signature mixte: cellule d'origine et oncopathogénie**
- **Génération combinée: score de méthylation, CNV et profil de méthylation MGMT**
- **Fichiers .idat facilement partageables**

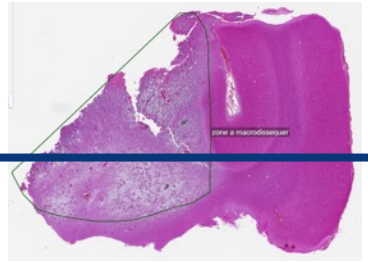
Intérêt dans cas complexes, ou données histo-radio-moléculaires discordantes

Tumeurs rares ou tumeurs émergentes

Reclassification de cohortes historiques



Limites



- **Importance de la cellularité**
- **Hiérarchisation des techniques en particulier si matériel exiguë/ biopsie**
- **Technique captive (Illumina, Nanopore)**
- **Algorithme/classifier Heidelberg non accessible, changement de versions**
- **Obtention de score non significatif (15%-20%) +++**
- **Erreur de score > 0,9 (< 0,5%)**
- **Ne renseigne pas sur altération moléculaire ciblable**

Published in final edited form as:
Acta Neuropathol. 2023 January ; 145(1): 71–82. doi:10.1007/s00401-022-02513-5.

Expanded analysis of high-grade astrocytoma with piloid features identifies an epigenetically and clinically distinct subtype associated with neurofibromatosis type 1

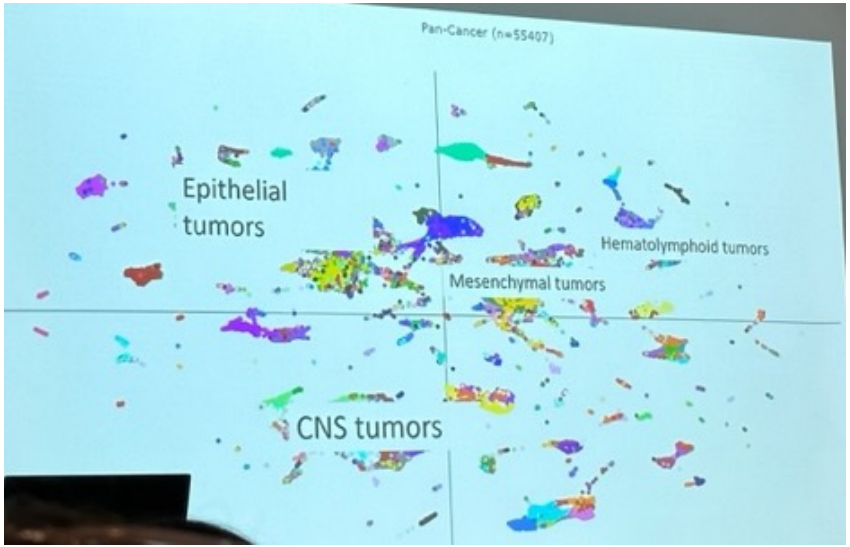
Neuropathol Appl Neurobiol. 2021 Apr;47(3):406-414. doi: 10.1111/nan.12683. Epub 2021 Jan 17.

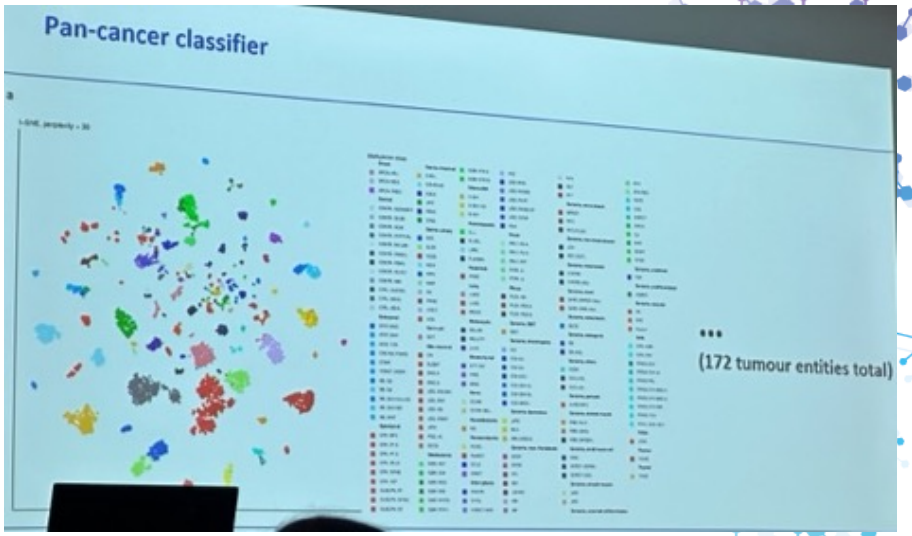
Accurate calling of KIAA1549–BRAF fusions from DNA of human brain tumours using methylation array–based copy number and gene panel sequencing data

Damian Stichel [1 2], Daniel Schrimpf [1 2], Philipp Sievers [1 2], Annekathrin Reinhardt [1 2], Abigail K Suwala [1 2], Martin Sill [3 4], David E Reuss [1 2], Andrey Korshunov [1 2 3], Belén M Casalini [1 2], Alexander C Sommerkamp [3 5 6], Jonas Ecker [3 7 8], Florian Selt [3 7 8], Dominik Sturm [3 5 7], Astrid Gnekow [9], Arend Koch [10 11], Michèle Simon [12], Pablo Hernáiz Driever [12], Ulrich Schüller [13 14 15], David Capper [10 11], Cornelis M van Tilburg [3 7 8], Olaf Witt [3 7 8], Till Milde [3 7 8], Stefan M Pfister [3 4 7], David T W Jones [3 5], Andreas von Deimling [1 2], Felix Sahm [1 2 3], Annika K Wefers [1 2 3 13 14 15]

Applications futures et challenges

- **Profil de méthylation PANCANCER**





NIH National Institutes of Health
Turning Discovery Into Health

dkfz.

Classification basée sur le profil de méthylation de l'ADN : challenges

- **Différents types d'algorithmes (RF, neural network)**
- **Différents training set**
- **Différents types de données (450K, EPIC V1 ou V2, Nanopore, WGBS, RRBS)**
  - Standardisation/ études comparatives/ accessibilité
  - Traçabilité des données utilisées +++ (set de référence, algorithme, type de matériel utilisé)

Applications futures et challenges

- **Profil de méthylation Oxford Nanopore (nanoDx)**

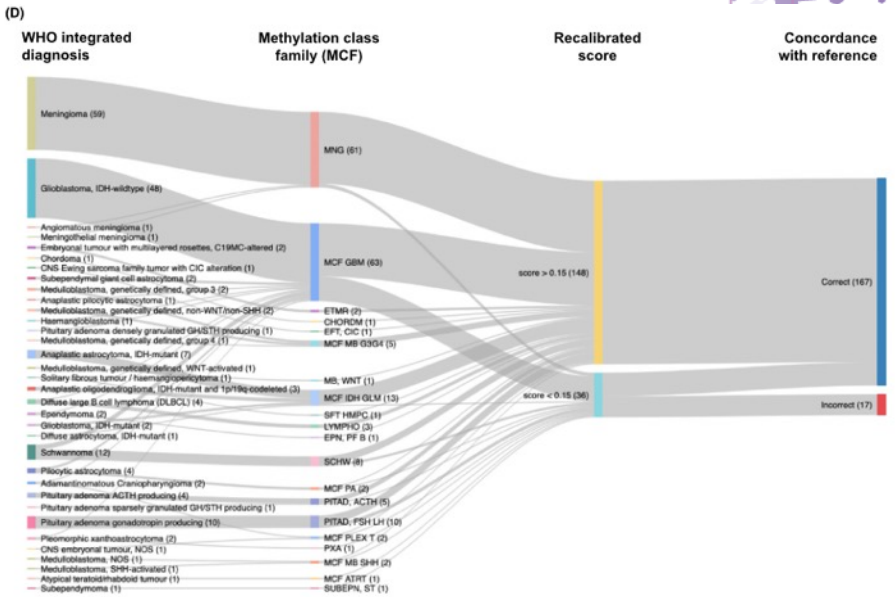
Received: 3 June 2021 | Revised: 28 August 2022 | Accepted: 2 October 2022
DOI: 10.1111/nan.12856

ORIGINAL ARTICLE

Neuropathology and Applied Neurobiology WILEY

Robust methylation-based classification of brain tumours using nanopore sequencing

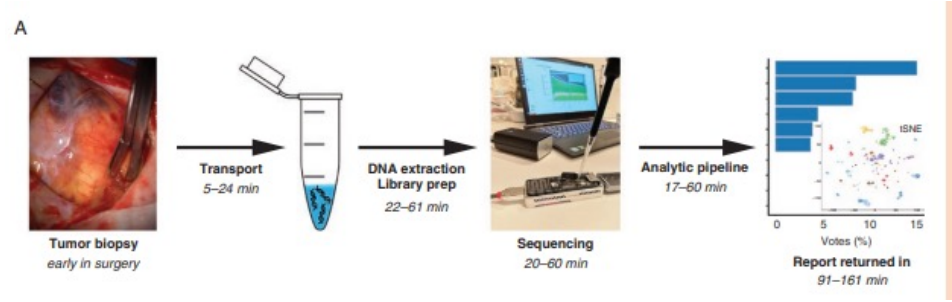
Luis P. Kuschel[1] | Jürgen Hench[2] | Stephan Frank[2] | Ivana Bratic Hench[2] |
Elodie Girard[3] | Maud Blanluet[3] | Julien Masliah-Planchon[3] | Martin Misch[4] |
Julia Onken[4] | Marcus Czabanka[4] | Dongsheng Yuan[1,5] | Sören Lukassen[5] |
Philipp Karau[5] | Naveed Ishaque[5] | Elisabeth G. Hain[6] | Frank Heppner[6] |
Ahmed Idbaih[7] | Nikolaus Behr[1] | Christoph Harms[1,8] | David Capper[6,9] |
Philipp Euskirchen[1,9]



Étude pilote
DNA natif, amplification et bisulfitation = 0
Données en temps réel

Applications futures et challenges

- **Profil de méthylation Oxford Nanopore (nanoDx)**



Neuro-Oncology Advances
3(1), 1–10, 2021 | https://doi.org/10.1093/noajnl/vdab149 | Advance Access date 10 October 2021

Intraoperative DNA methylation classification of brain tumors impacts neurosurgical strategy

Luna Djirackor[†], Skarphedinn Halldorsson[†], Pitt Niehusmann, Henning Leske, David Capper, Luis P. Kuschel, Jens Pahnke, Bernt J. Due-Tønnessen, Iver A. Langmoen, Cecilie J. Sandberg, Philipp Euskirchen[‡] and Einar O. Vik-Mo[‡]

Acta Neuropathologica (2022) 143:609–612
https://doi.org/10.1007/s00401-022-02415-6

CORRESPONDENCE

Rapid-CNS^2: rapid comprehensive adaptive nanopore-sequencing of CNS tumors, a proof-of-concept study

Areeba Patel[1,2] · Helin Dogan[1,2] · Alexander Payne[3] · Elena Krause[1] · Philipp Sievers[1,2] · Natalie Schoebe[1,2] · Daniel Schrimpf[1,2] · Christina Blume[1,2] · Damian Stichel[1,2] · Nadine Holmes[3] · Philipp Euskirchen[4] · Jürgen Hench[5] · Stephan Frank[5] · Violaine Rosenstiel-Goidts[6] · Miriam Ratliff[7] · Nima Etminan[7] · Andreas Unterberg[8] · Christoph Dieterich[9] · Christel Herold-Mende[8] · Stefan M. Pfister[10,11,12] · Wolfgang Wick[14,15] · Matthew Loose[3] · Andreas von Deimling[1,2] · Martin Sill[10,11] · David T. W. Jones[10,13] · Matthias Schlesner[16] · Felix Sahm[1,2,10]

Article

Ultra-fast deep-learned CNS tumour classification during surgery

https://doi.org/10.1038/s41586-023-06615-2
Received: 10 February 2023
Accepted: 6 September 2023

C. Vermeulen[1,2,6], M. Pagès-Gallego[1,2,6], L. Kester[3], M. E. G. Kranendonk[3], P. Wesseling[3,4], N. Verburg[5], P. de Witt Hamer[5], E. J. Kooi[4], L. Dankmeijer[4,5], J. van der Lugt[3], K. van Baarsen[3], E. W. Hoving[3], B. B. J. Tops[3] & J. de Ridder[1,2]

Simulation *in silico* Sturgeon
Surpasse classifier DKFZ V11.4
Diagnostic moléculaire en 90 mn

Vermeulen C *et al. Nature* 2023 Oct,622

Applications futures et challenges

- **Profil de méthylation Nanopore sur LCR (nano CSF) et prélèvements sanguins**

› Clin Chem. 2023 Aug 25:hvad115. doi: 10.1093/clinchem/hvad115. Online ahead of print.

Classification of Brain Tumors by Nanopore Sequencing of Cell-Free DNA from Cerebrospinal Fluid

Ann-Kristin Afflerbach [1 2], Christian Rohrandt [3], Björn Brändl [4], Marthe Sönksen [1], Jürgen Hench [5], Stephan Frank [5], Daniela Börnigen [6], Malik Alawi [6], Martin Mynarek [1], Beate Winkler [1], Franz Ricklefs [7], Michael Synowitz [8], Lasse Dührsen [7], Stefan Rutkowski [1], Annika K Wefers [9 10], Franz-Josef Müller [4 11], Melanie Schoof [1 2], Ulrich Schüller [1 2 9]

2078 Neuro-Oncology
24(12), 2078–2090, 2022 | https://doi.org/10.1093/neuonc/noac127 | Advance Access date 12 May 2022

Diagnostic potential of extracellular vesicles in meningioma patients

Franz L. Ricklefs, Cecile L. Maire, Kathrin Wollmann, Lasse Dührsen, Krystian D. Fita, Felix Sahm, Christel Herold-Mende, Andreas von Deimling, Katharina Kolbe, Mareike Holz, Leonie Bergmann, Marceline M. Fuh, Hartmut Schlüter, Malik Alawi, Rudolph Reimer, Sven Peine, Markus Glatzel, Manfred Westphal, and Katrin Lamszus

1126 Neuro-Oncology
24(7), 1126–1139, 2022 | https://doi.org/10.1093/neuonc/noac050 | Advance Access date 25 February 2022

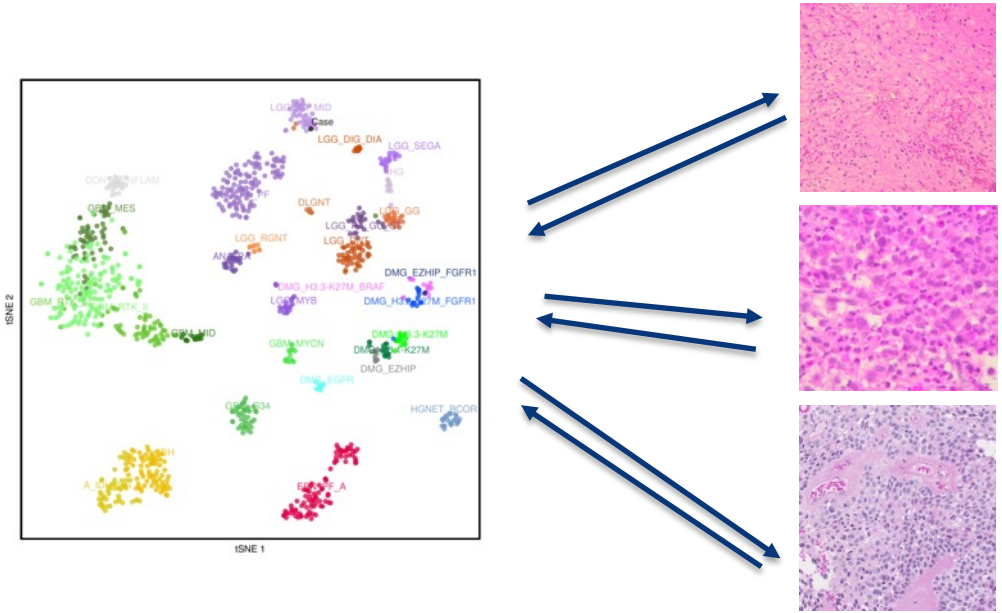
Detection of tumor-specific DNA methylation markers in the blood of patients with pituitary neuroendocrine tumors

Grayson A. Herrgott, Karam P. Asmaro, Michael Wells, Thais S. Sabedot, Tathiane M. Malta, Maritza S. Mosella, Kevin Nelson, Lisa Scarpace, Jill S. Barnholtz-Sloan, Andrew E. Sloan, Warren R. Selman, Ana C. deCarvalho, Laila M. Poisson, Abir Mukherjee, Adam M. Robin, Ian Y. Lee, James Snyder, Tobias Walbert, Mark Rosenblum, Tom Mikkelsen, Arti Bhan, John Craig, Steven Kalkanis, Jack Rock, Houtan Noushmehr, and Ana Valeria Castro

Plasma
Extracellular vesicules (EV)
EV-DNA methylation array 850K // DNA methylation MNG
Diagnostic and monitoring tool

Applications futures et challenges

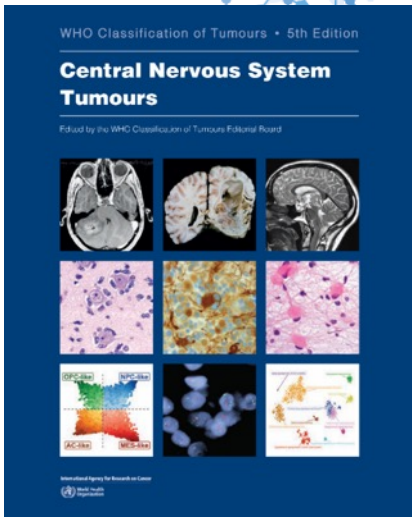
- **Classes de méthylation et IA pathologie digitale**



- **Profils de méthylation en dehors de l'oncologie (pathologie neuro-développementale, neurodégénerative, psychiatrique, etc.**

CONCLUSION

- **Méthylome/ IA : un outil révolutionnaire en neuro-oncopathologie**
- **Première étape vers l'utilisation des signatures épigénétiques via d'autres technologies (Nanopore, ddPCR)**
- **Première étape vers l'utilisation d'autres algorithmes (Bethesda, etc.) ou d'autres technologies d'analyses (tSNE, UMAP)**
- **Première étape vers l'utilisation d'autres types de matériel biologique (LCS, ADNc, urine)**



Dr Julien Masliah-Planchon, Institut Curie

Dr Raphael Saffroy, Paul Brousse

Pr Anne-Sophie Lebre, CHU Reims

MERCI DE VOTRE ATTENTION

Neuro-Oncology

23(S5), S16–29, 2021 | https://doi.org/10.1093/neuonc/noab143

DNA methylation profiling as a model for discovery and precision diagnostics in neuro-oncology

Drew Pratt, Felix Sahm, and Kenneth Aldape

Department of Pathology, University of Michigan, Ann Arbor, Michigan, USA (D.W.); Department of Neuropathology, Institute of Pathology, University Hospital Heidelberg, Heidelberg, Germany (F.S.); Laboratory of Pathology, Center for Cancer Research, National Cancer Institute, Bethesda, Maryland, USA (K.A.)

Acta Neuropathologica
https://doi.org/10.1007/s00401-023-02596-8

ORIGINAL PAPER

From methylation to myelination: epigenomic and transcriptomic profiling of chronic inactive demyelinated multiple sclerosis lesions

Assia Tiane[1,2,3] · Melissa Schepers[1,2,3] · Rick A. Reijnders[2] · Lieve van Veggel[1,2,3] · Sarah Chenine[1,2,3] · Ben Rombaut[1,2,3] · Emma Dempster[4] · Catherine Verfaillie[5] · Kobi Wasner[6] · Anne Grünewald[6,7] · Jos Prickaerts[2] · Ehsan Pishva[2,4] · Niels Hellings[3,8] · Daniel van den Hove[2,9] · Tim Vanmierlo[1,2,3]

Received: 6 March 2023 / Revised: 1 June 2023 / Accepted: 1 June 2023

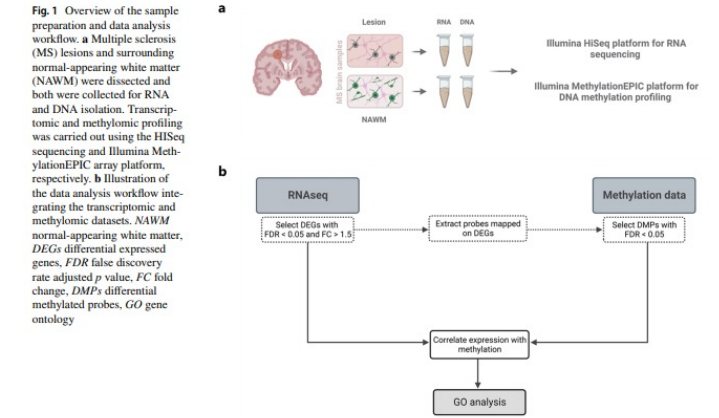


Fig. 1 Overview of the sample preparation and data analysis workflow. **a** Multiple sclerosis (MS) lesions and surrounding normal-appearing white matter (NAWM) were dissected and both were collected for RNA and DNA isolation. Transcriptomic and methylomic profiling was carried out using the HiSeq sequencing and Illumina MethylationEPIC array platform, respectively. **b** Illustration of the data analysis workflow integrating the transcriptomic and methylomic datasets. *NAWM* normal-appearing white matter, *DEGs* differential expressed genes, *FDR* false discovery rate adjusted *p* value, *FC* fold change, *DMPs* differential methylated probes, *GO* gene ontology

Acta Neuropathologica (2023) 146:77–95
https://doi.org/10.1007/s00401-023-02583-z

ORIGINAL PAPER

Brain DNA methylomic analysis of frontotemporal lobar degeneration reveals *OTUD4* in shared dysregulated signatures across pathological subtypes

Katherine Fodder[1,2] · Megha Murthy[1,3] · Patrizia Rizzu[4] · Christina E. Toomey[1,3,5] · Rahat Hasan[6] · Jack Humphrey[6] · Towfique Raj[6] · Katie Lunnon[7] · Jonathan Mill[7] · Peter Heutink[4,8] · Tammaryn Lashley[1,2] · Conceição Bettencourt[1,2]

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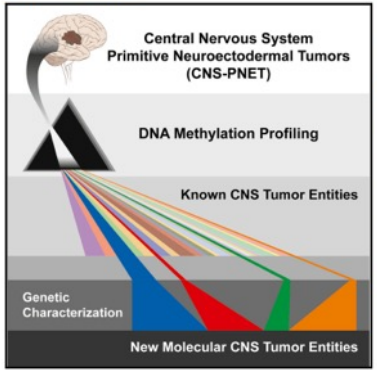
Cell

2016

New Brain Tumor Entities Emerge from Molecular Classification of CNS-PNETs

Graphical Abstract



Authors
Dominik Sturm, Brent A. Orr, Umut H. Toprak, ..., David W. Ellison, Andrey Korshunov, Marcel Kool

Correspondence
m.kool@dkfz.de

In Brief
Highly malignant primitive neuroectodermal tumors of the CNS (CNS-PNETs) have been challenging to diagnose and distinguish from other kinds of brain tumors, but molecular profiling now reveals that these cancers can be readily classified into some known tumor types and four new entities with distinct histopathological and clinical features, paving the way for meaningful clinical trials.

Nature. 2018 Mar 22;555(7697):469-474. doi: 10.1038/nature26000. Epub 2018 Mar 14.

DNA methylation-based classification of central nervous system tumours

David Capper [1 2 3 4], David T W Jones [5 6], Martin Sill [5 6 7], Volker Hovestadt [8],

Nat Commun. 2021 Jan 21;12(1):498. doi: 10.1038/s41467-020-20603-4.

Sarcoma classification by DNA methylation profiling

Christian Koelsche [# 1 2 3], Daniel Schrimpf [# 1 2], Damian Stichel [# 2], Martin Sill [# 4 5],

Multicenter Study Lancet Oncol. 2016 Oct;17(10):1386-1395.
doi: 10.1016/S1470-2045(16)30297-2. Epub 2016 Aug 27.

Epigenetic profiling to classify cancer of unknown primary: a multicentre, retrospective analysis

Sebastian Moran [1], Anna Martínez-Cardús [1], Sergi Sayols [1], Eva Musulén [2], Carme Balañá [3],

nature communications

Article

https://doi.org/10.1038/s41467-022-34815-3

DNA methylation-based classification of sinonasal tumors

Received: 31 March 2022

Accepted: 7 November 2022

Published online: 28 November 2022

Check for updates

A list of authors and their affiliations appears at the end of the paper

The diagnosis of sinonasal tumors is challenging due to a heterogeneous spectrum of various differential diagnoses as well as poorly defined, disputed entities such as sinonasal undifferentiated carcinomas (SNUCs). In this study, we apply a machine learning algorithm based on DNA methylation patterns to classify sinonasal tumors with clinical-grade reliability. We further show that sinonasal tumors with SNUC morphology are not as undifferentiated as their current terminology suggests but rather reassigned to four distinct molecular classes defined by epigenetic, mutational and proteomic profiles. This includes two classes with neuroendocrine differentiation, characterized by *IDH2* or *SMARCA4/ARID1A* mutations with an overall favorable clinical course, one class composed of highly aggressive SMARCB1-deficient carcinomas and another class with tumors that represent potentially previously misclassified adenoid cystic carcinomas. Our findings can aid in improving the diagnostic classification of sinonasal tumors and could help to change the current perception of SNUCs.

nature medicine

Article

https://doi.org/10.1038/s41591-023-02255-1

Multiomic neuropathology improves diagnostic accuracy in pediatric neuro-oncology

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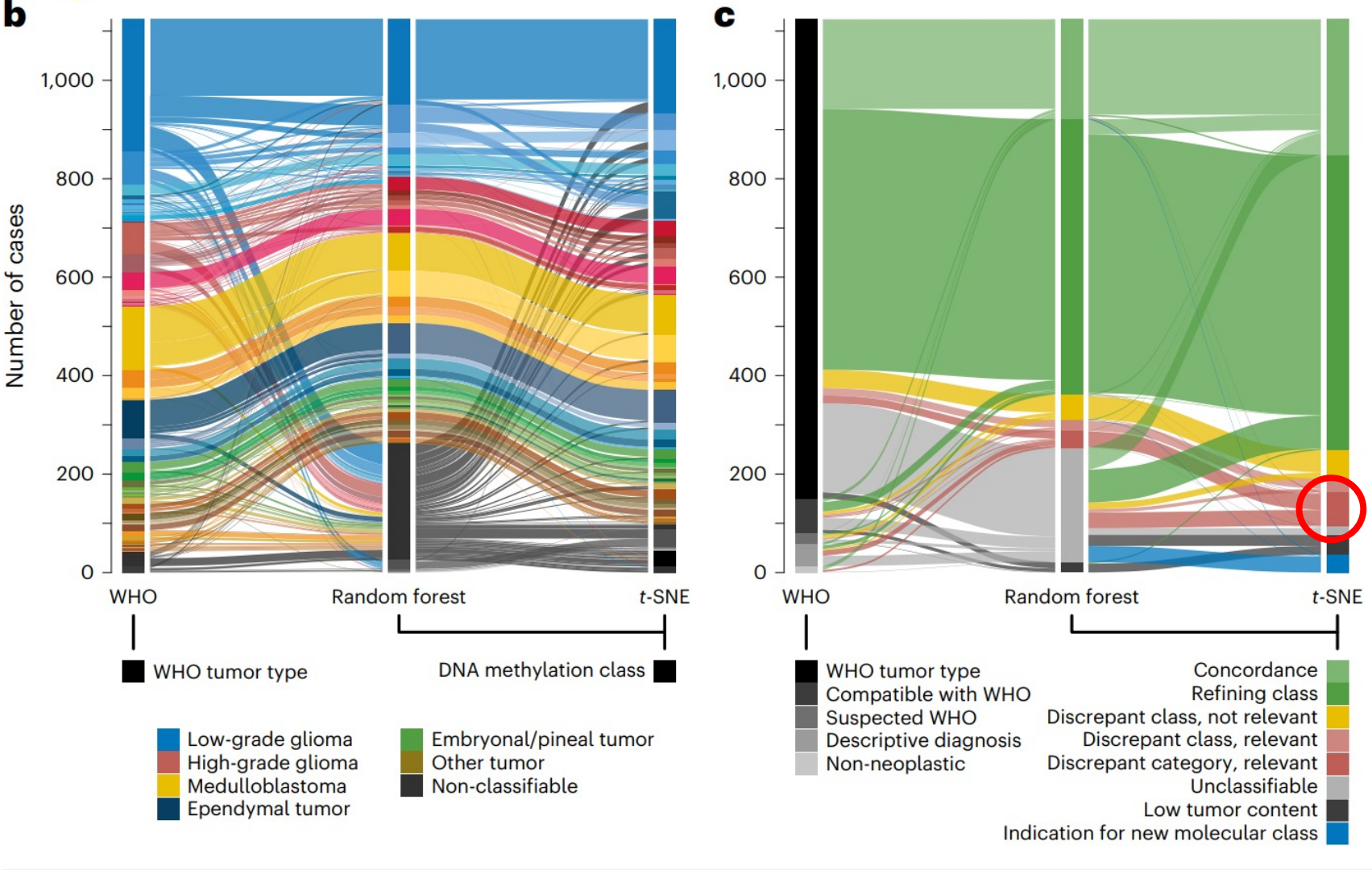
Accepted: 13 February 2023

Dominik Sturm[1,2,3], David Capper[4,5], Felipe Andreiuolo[6,7,8], Marco Gessi[6], Christian Kölsche[9], Annekathrin Reinhardt[10], Philipp Sievers[10], Annika K. Wefers[11], Azadeh Ebrahimi[6,10,12], Abigail K. Suwala[10,12,13], Gerrit H. Gielen[6], Martin Sill[1,14], Daniel Schrimpf[10], Damian Stichel[10,12], Volker Hovestadt[15,16], Bjarne Daenekas[4,15,16], Agata Rode[1,2], Stefan Hamelmann[10,12], Christopher Previti[1,14], Natalie Jäger[1,14], Ivo Buchhalter[17], Mirjam Blattner-Johnson[1,2], Barbara C. Jones[1,2,3], Monika Warmuth-Metz[18,19], Brigitte Bison[19,20], Kerstin Grund[21], Christian Sutter[21], Steffen Hirsch[1,14,21], Nicola Dikow[21], Martin Hasselblatt[22], Ulrich Schüller[11,23,24], Nicolas U. Gerber[25], Christine L. White[26,27,28], Molly K. Buntine[26,27], Kathryn Kinross[29], Elizabeth M. Algar[26,27,30], Jordan R. Hansford[31], Nicholas G. Gottardo[32,33,34], Pablo Hernáiz Driever[35], Astrid Gnekow[36], Olaf Witt[1,3,37], Hermann L. Müller[38], Gabriele Calaminus[39], Gudrun Fleischhack[40], Uwe Kordes[23], Martin Mynarek[23,41], Stefan Rutkowski[23], Michael C. Frühwald[36], Christof M. Kramm[42], Andreas von Deimling[10,12], Torsten Pietsch[6,43], Felix Sahm[1,10,12,43], Stefan M. Pfister[1,3,14,43] & David. T. W. Jones[1,2,43]

Étude prospective nationale
2015-2019
1200 patients pédiatriques

Matériel insuffisant : 4%
Score < 0,9 = 15% en V12.5


b
c
Number of cases
1,000
800
600
400
200
0
WHO
Random forest
t-SNE
WHO tumor type
DNA methylation class
Low-grade glioma
High-grade glioma
Medulloblastoma
Ependymal tumor
Embryonal/pineal tumor
Other tumor
Non-classifiable
WHO tumor type
Compatible with WHO
Suspected WHO
Descriptive diagnosis
Non-neoplastic
Concordance
Refining class
Discrepant class, not relevant
Discrepant class, relevant
Discrepant category, relevant
Unclassifiable
Low tumor content
Indication for new molecular class

Neuro-Oncology
24(4), 571–581, 2022 | https://doi.org/10.1093/neuonc/noab227 | Advance Access date 23 September 2021

Impact of the methylation classifier and ancillary methods on CNS tumor diagnostics

Zhichao Wu,[†] Zied Abdullaev,[†] Drew Pratt, Hye-Jung Chung, Shannon Skarshaug, Valerie Zgonc, Candice Perry, Svetlana Pack, Lola Saidkhodjaeva, Sushma Nagaraj, Manoj Tyagi, Vineela Gangalapudi, Kristin Valdez, Rust Turakulov, Liqiang Xi, Mark Raffeld, Antonios Papanicolau-Sengos, Kayla O'Donnell, Michael Newford, Mark R. Gilbert, Felix Sahm, Abigail K. Suwala, Andreas von Deimling, Yasin Mamatjan, Shirin Karimi, Farshad Nassiri, Gelareh Zadeh, Eytan Ruppin, Martha Quezado, and Kenneth Aldape

1258 CNS tumors

Methyloma indication

- Unclassifiable tumors, complex situation
- Suspected diagnosis requiring multiple successive techniques or techniques not available on site

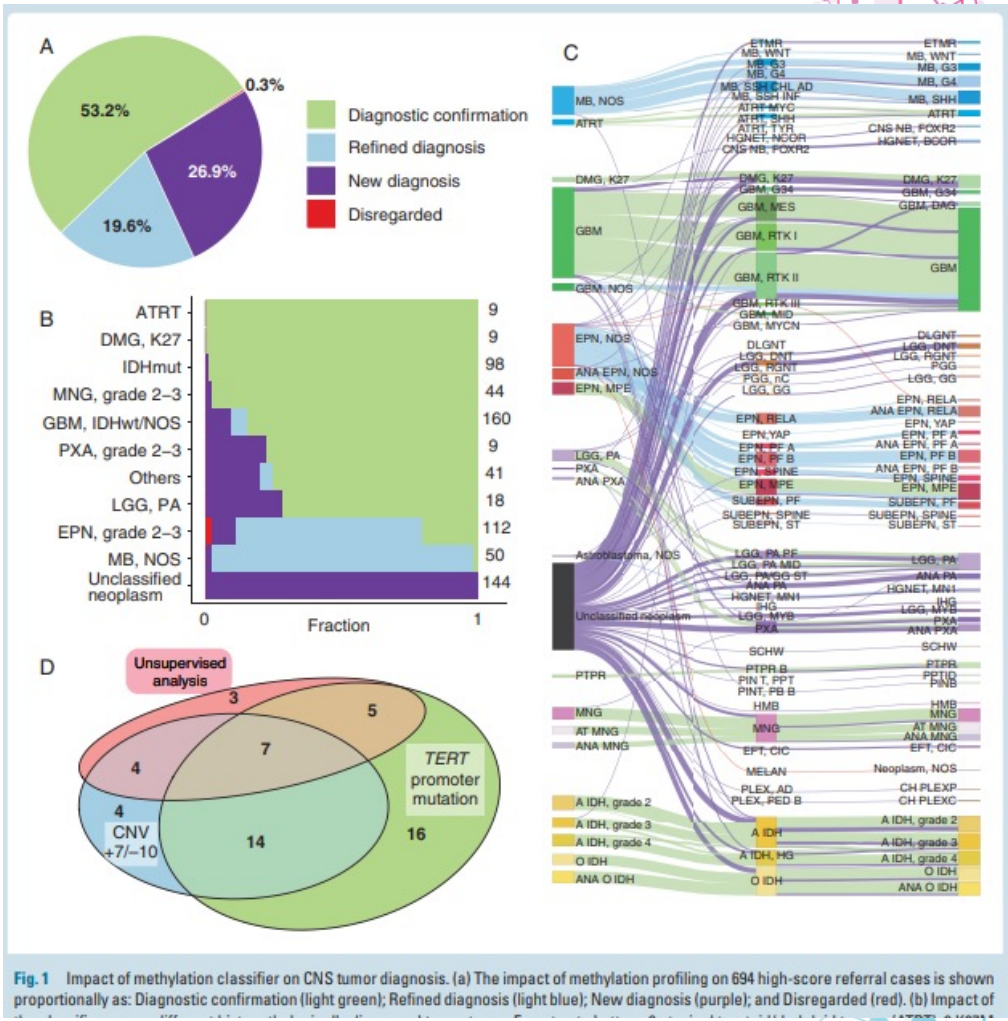


Fig. 1 Impact of methylation classifier on CNS tumor diagnosis. (a) The impact of methylation profiling on 694 high-score referral cases is shown proportionally as: Diagnostic confirmation (light green); Refined diagnosis (light blue); New diagnosis (purple); and Disregarded (red). (b) Impact of

Sample upload

Classification using methylation profiling is a research tool under development, it is not verified and has not been clinically validated. Implementation of the results in a clinical setting is in the sole responsibility of the treating physician.

Sample Name (mandatory)

The sample name

Diagnosis (mandatory)

The diagnisis of the sample

Location (mandatory)

Sample location

Age (empty or a number (integer))

Age

Gender (optional)

The gender (eg. NA, male, female)

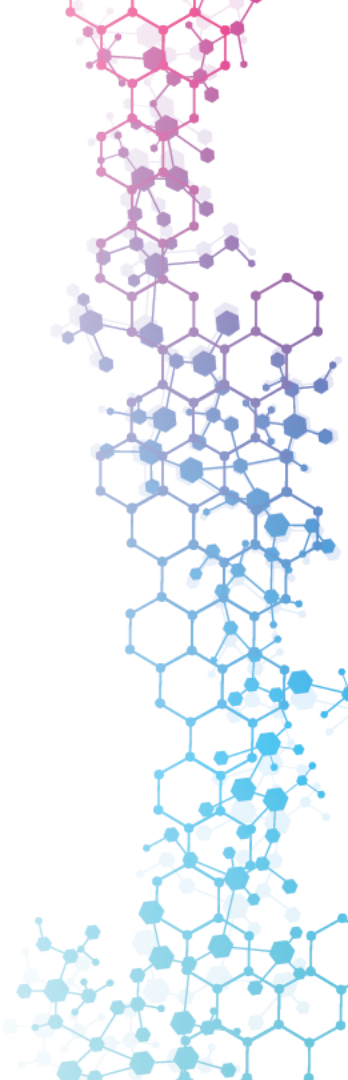
Notes (optional)

Notes

Chip type (optional)

Chip-type (eg. 450K, EPIC)

Sample type (mandatory)



Merci de votre attention

Avec la participation scientifique du GFCO

9e ÉDITION

JOURNÉES DU **GFCO 2023**

Biomarqueurs et analyses moléculaires en oncologie

Avec la participation scientifique du GFCO