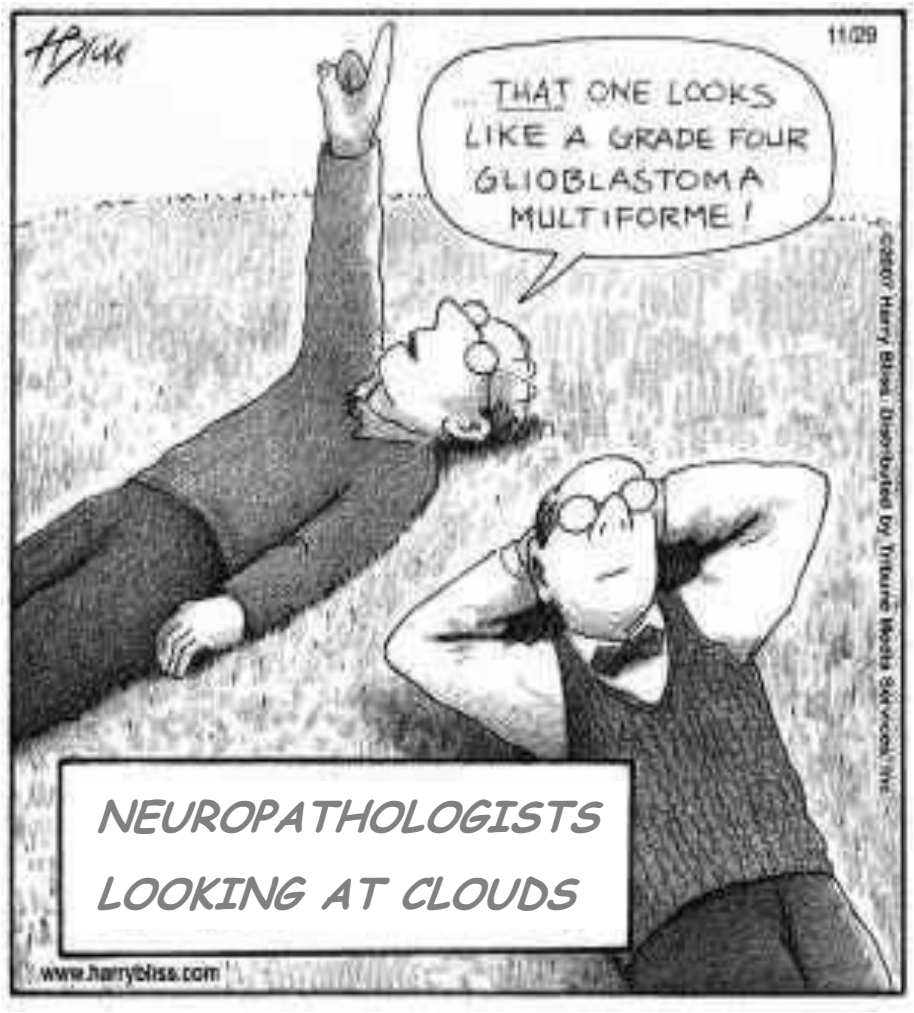
MASSACHUSETTS GENERAL HOSPITAL
PATHOLOGY

Advancing Diagnosis and Discovery



WHO's next?

Suggested guidelines for the next WHO classification of brain tumors

David N. Louis, M.D.

Pathologist-in-Chief, MGH
Benjamin Castleman Professor of Pathology, HMS

Outline

- Background on WHO classifications
- Challenges and opportunities for the next WHO classification of nervous system tumors
- The Haarlem meeting and its recommendations
- Next steps for the forthcoming WHO update and a glimpse at future classification systems

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Accurate classification of human neoplasms

- care of individual patients (estimating prognosis, guiding therapy)
- conduct and interpretation of clinical trials
- analysis and understanding of experimental studies
- elucidation of population-based disease trends that may implicate particular etiologies
- allocation of resources by governments and health insurers to support health care

Periodic revisions of tumor classifications therefore have diverse and important effects on many aspects of individual and population health

“Periodic”: ICD

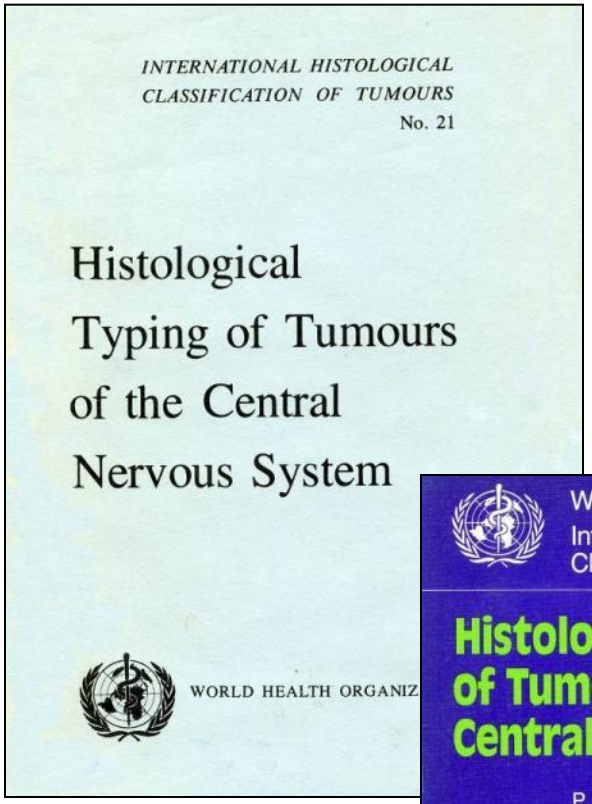
- ICD (WHO): revisions at ~10-yr intervals, with minor revisions at ~3-yr intervals
- ICD-9 released in 1977
- ICD-10 released in 1992
- ICD-11 estimated to be released in 2015
- ICD-O (Oncology)
  - [CNS WHO 2007 → 2014 and 2015]
- SNOMED (IHTSDO-based)

Early history of WHO tumor classifications

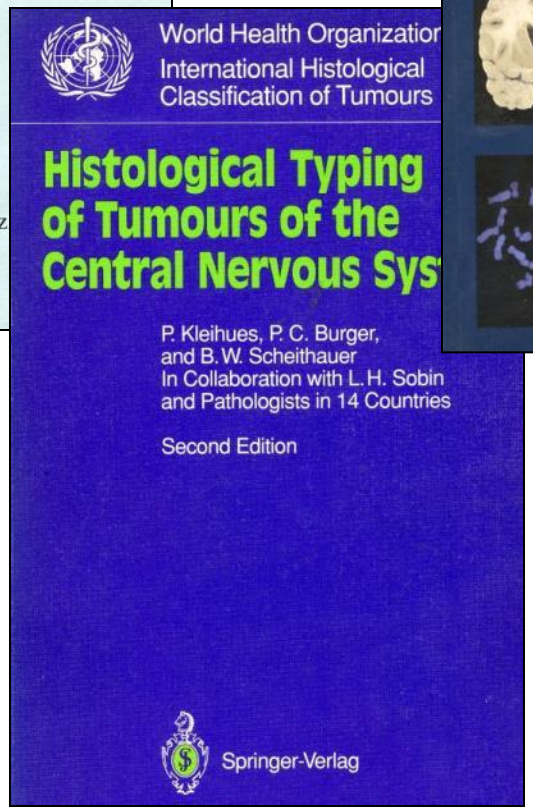
- 1952: WHO Expert Committee on Health Statistics advocates general principles to govern statistical classification of tumors: 1) anatomic site; 2) histological type; 3) degree of malignancy

- 1956: WHO Executive Board resolution to establish centers for collection and classification of human cancer tissues; endorsed in 1957; centers established from 1958 onward

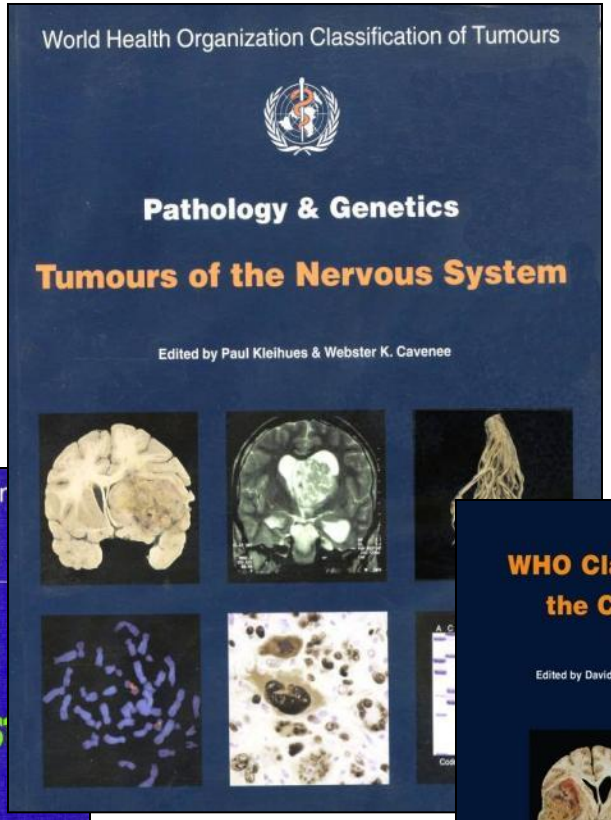
- 1967-1981: Publications of first editions of the International Histological Classification of Tumours



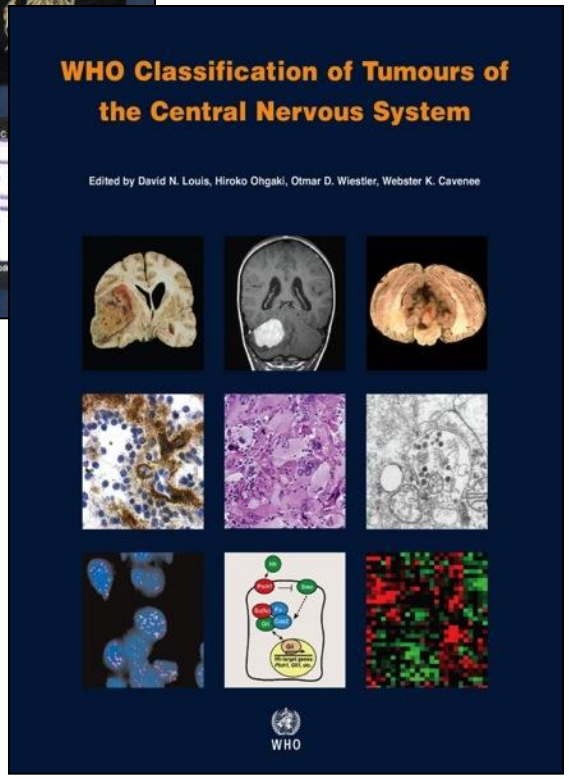
1979



1993



2000



2007

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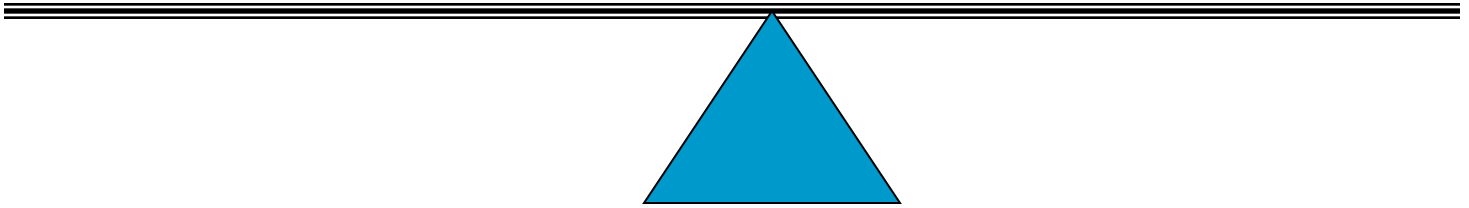
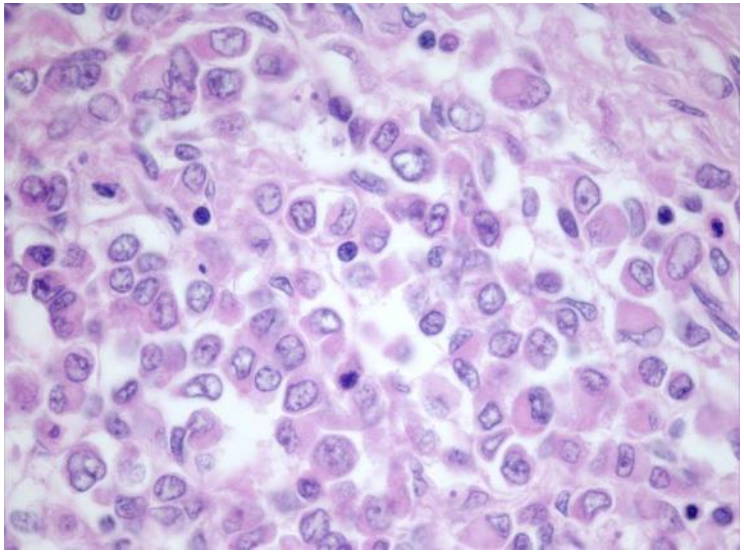
Periodicity: different perspectives and needs

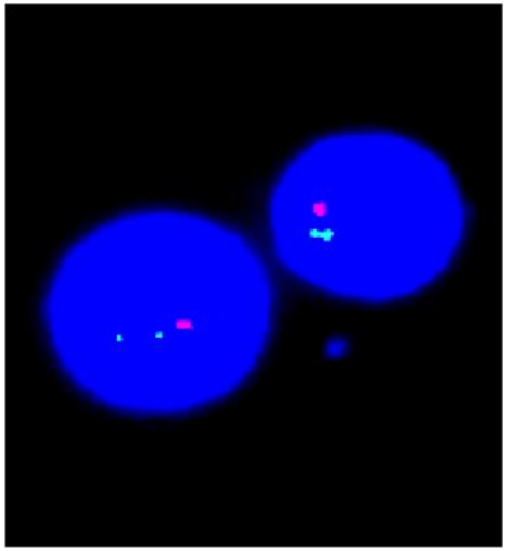
- Incorporate the latest molecular signatures
- Utilize the most accurate, cutting-edge techniques

- Do not disrupt current clinical diagnosis and patient management
- Weigh the availability and cost of novel diagnostic techniques
- Preserve the ability for long-term clinical, experimental and etiological correlations



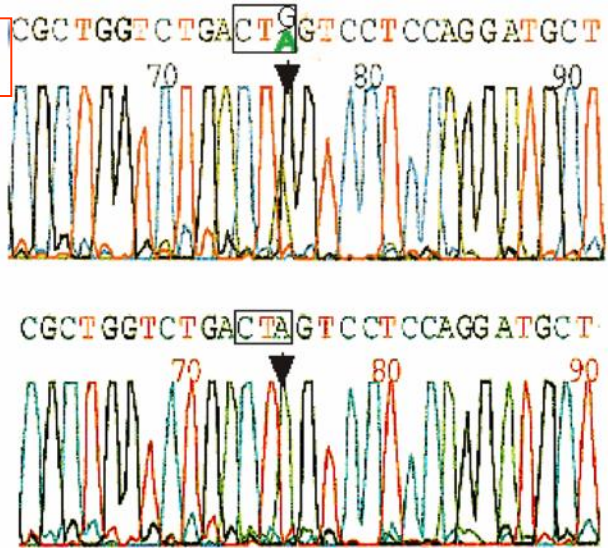
Pace of change 1: atypical teratoid/rhabdoid tumor (ATRT) dx

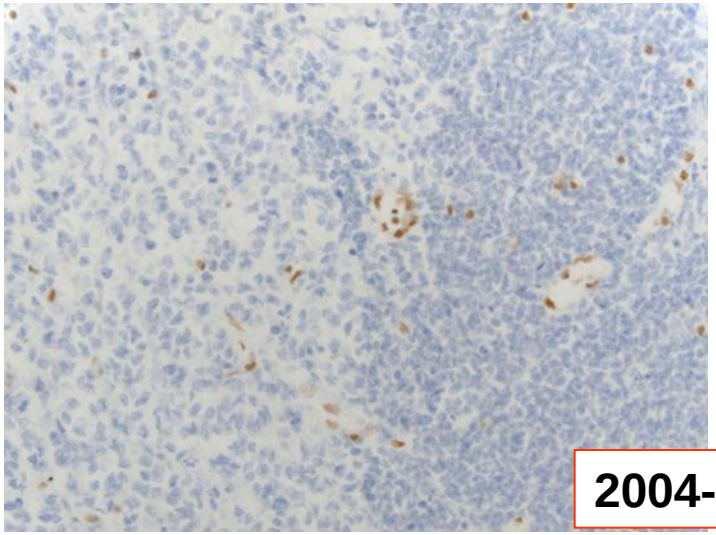




1992-1995

1998-2000





2004-2005

FISH and sequencing courtesy of Jaclyn Biegel

Histology and immunohistochemistry courtesy of Alexander R. Judkins

Pace of change 2: *IDH1* mutation and malignant glioma

Sciencexpress / www.sciencexpress.org / 4 September 2008 / Page 1 / 10.1126/science.1164382

Sept 2008

Sciencexpress Research Article

An Integrated Genomic Analysis of Human Glioblastoma Multiforme

D. Williams Parsons,[1,2*] Siân Jones,[1*] Xiaosong Zha[1*] Jimmy Cheng Ho Lin[1*] Rebecca J. Leary[1*]
Philipp Angenendt,[1*] Parminder Mankoo,[3] Hannah
Roger McLendon,[5] B. Ahmed Rasheed,[5] Stephen K
Busam,[8] Hanna Tekleab,[8] Luis A. Diaz Jr.,[1] James F
Kazue Nagahashi Marie,[10] Sueli Mieko Oba Shinjo
Rachel Karchin,[3] Nick Papadopoulos,[1] Giovanni Pa
Kenneth W. Kinzler[1†]

Acta Neuropathol
DOI 10.1007/s00401-009-0595-z
Received: 23 September 2009 / Accepted: 23 September 2009

SHORT REPORT

Sept 2009

Monoclonal antibody specific for *IDH1* R132H mutation

David Capper · Hanswalter Zentgraf · Jörg Balss · Christian Hartmann · Andreas von Deimling

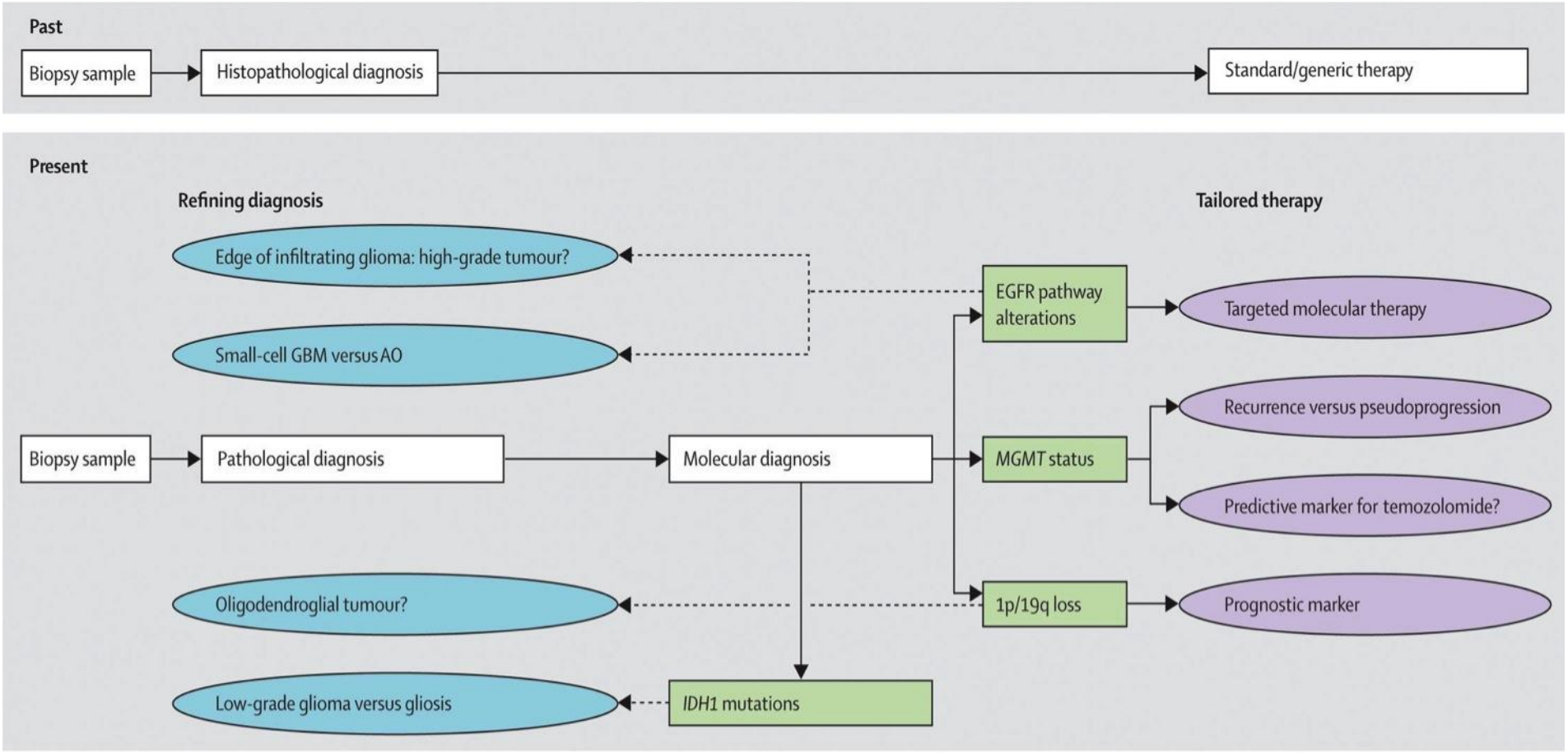
Acta Neuropathol
DOI 10.1007/s00401-009-0632-y
Received: 20 December 2009 / Revised: 21 December 2009 / Accepted: 21 December 2009

CORRESPONDENCE

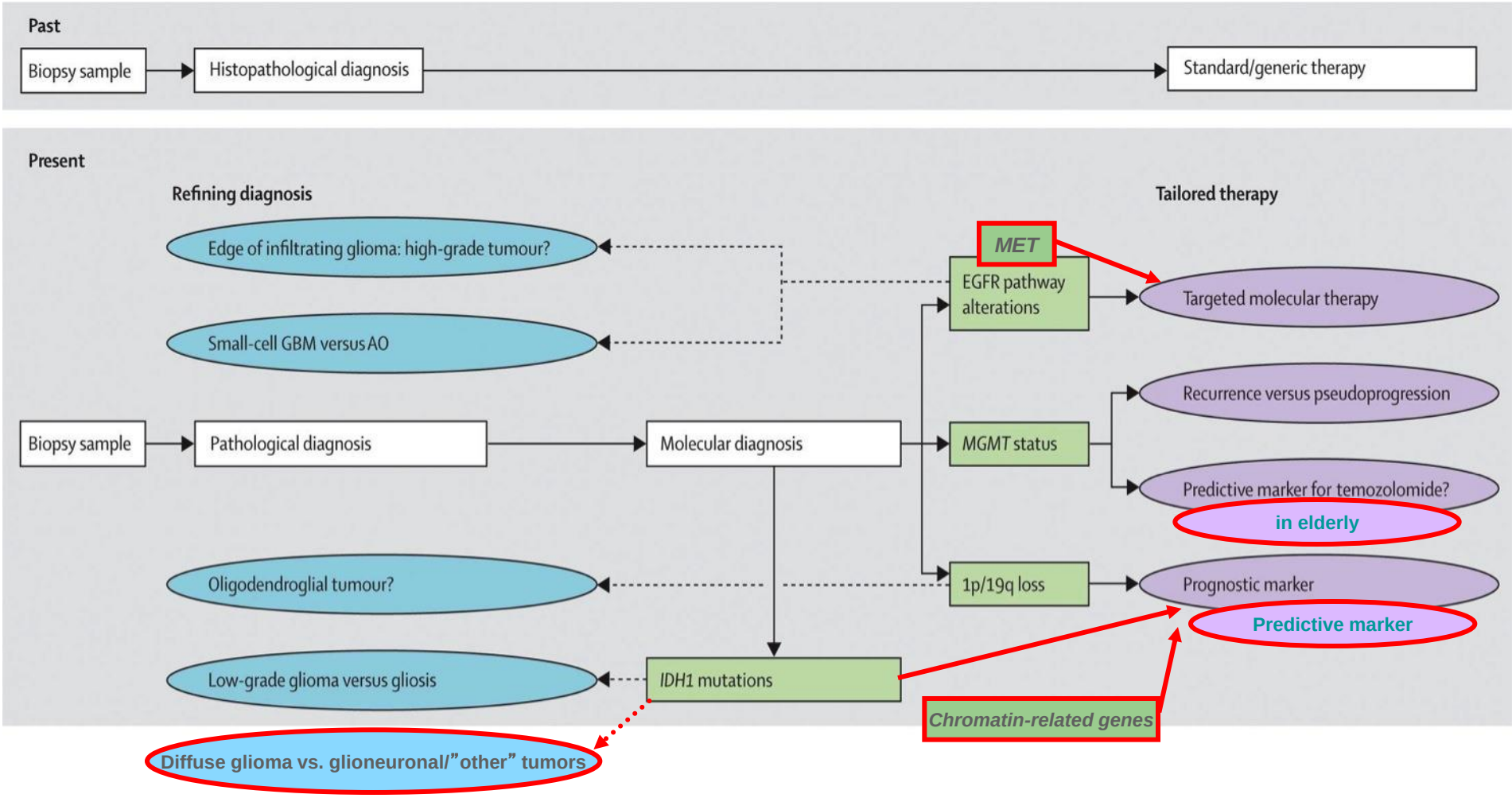
Dec 2009

Mutant IDH1-specific immunohistochemistry distinguishes diffuse astrocytoma from astrocytosis

Sandra Camelo-Piragua · Michael Jansen · Aniruddha Ganguly · J. ChulMin Kim · David N. Louis · Catherine L. Nutt



Jansen, Yip and Louis, *Lancet Neurol* 2010



Jansen, Yip and Louis, *Lancet Neurol* 2010

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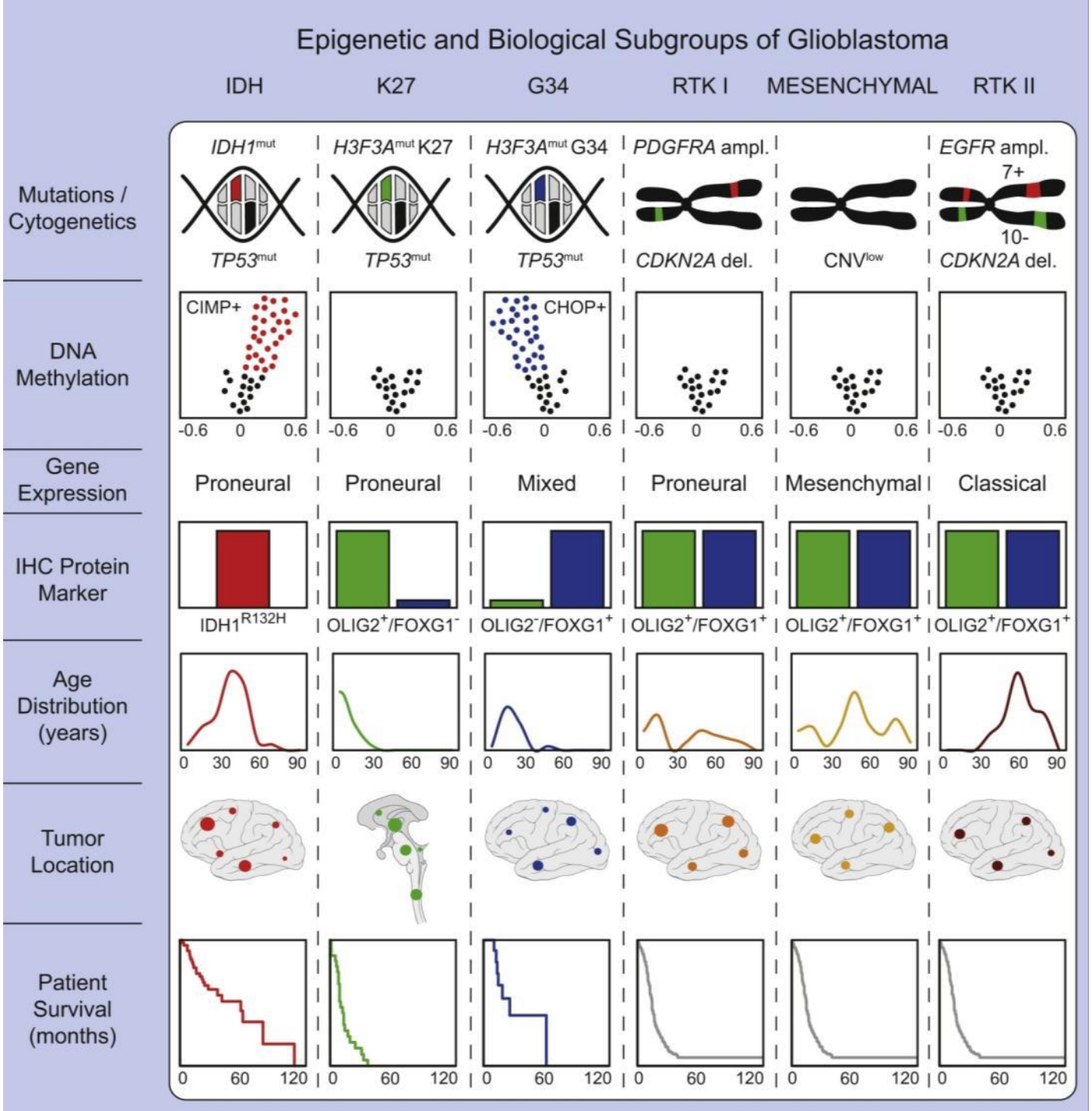
The age of the splitters

- “Is there an official figure of how many tumor entities exist currently? I guess the WHO classification is the best source, however, I want to know the number of tumors in all organ systems included. Can anyone please help?”
- “Well, I spent yesterday counting and the lumpers come up with 21 and the splitters come up with 104,537 currently.”

SDN, April 7, 2014

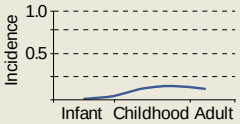
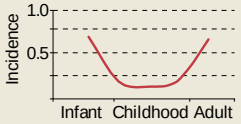
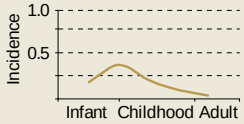
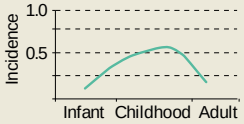
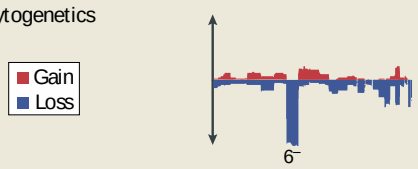
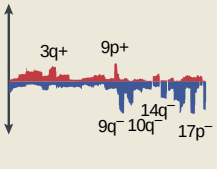
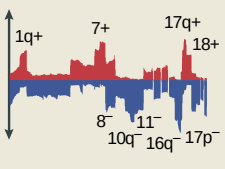
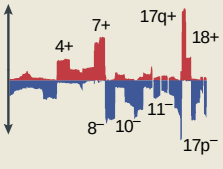


Sturm et al.

Hotspot mutations in H3F3A and IDH1 define distinct epigenetic and biological subgroups of glioblastoma

Cancer Cell 2012

Table 1 | Clinical and genomic features of medulloblastoma subgroups*

	WNT (~10%)	SHH (~30%)	Group 3 (~25%)	Group 4 (~35%)
Clinical features				
Gender ratio (M/F)	~1/1	~1.5/1	~2/1	~3/1
Age distribution				
Histology	Classic; very rare LCA	Classic > desmoplastic/ nodular > LCA > MBEN	Classic > LCA	Classic; rarely LCA
Metastasis at diagnosis	~5–10%	~15–20%	~40–45%	~35–40%
Overall survival (5 years)	~95%	~75%	~50%	~75%
Proposed cell of origin	Lower rhombic lip progenitor cells	CGNPs of the EGL and cochlear nucleus; neural stem cells of the SVZ	Prominin 1$^+$, lineage$^-$ neural stem cells; CGNPs of the EGL	Unknown
Genomic features				
Cytogenetics				
Driver genes‡	• *CTNNB1* (90.6%) • *DDX3X* (50%) • *SMARCA4* (26.3%) • *MLL2* (12.5%) • *TP53* (12.5%)	• *PTCH1* (28%) • *TP53* (13.6%) • *MLL2* (12.9%) • *DDX3X* (11.7%) • *MYCN* (8.2%) • *BCOR* (8%) • *LDB1* (6.9%) • *TCF4* (5.5%) • *GLI2* (5.2%)	• *MYC* (16.7%) • *PVT1* (11.9%) • *SMARCA4* (10.5%) • *OTX2* (7.7%) • *CTDNEP1* (4.6%) • *LRP1B* (4.6%) • *MLL2* (4%)	• *KDM6A* (13%) • *SNCAIP* (10.4%) • *MYCN* (6.3%) • *MLL3* (5.3%) • *CDK6* (4.7%) • *ZMYM3* (3.7%)
Expression signature	WNT signalling	SHH signalling	• MYC signature • Retinal signature	Neuronal signature

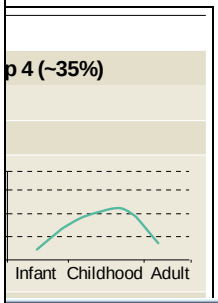
Medulloblastomics: the end of the beginning

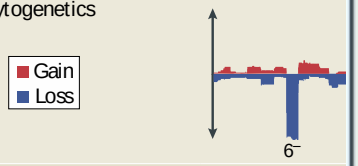
Paul A. Northcott[1], David T. W. Jones[1], Marcel Kool[1], Giles W. Robinson[2], Richard J. Gilbertson[2], Yoon-Jae Cho[3], Scott L. Pomeroy[4,5], Andrey Korshunov[6], Peter Lichter[7], Michael D. Taylor[8,9,10] and Stefan M. Pfister[1,11]

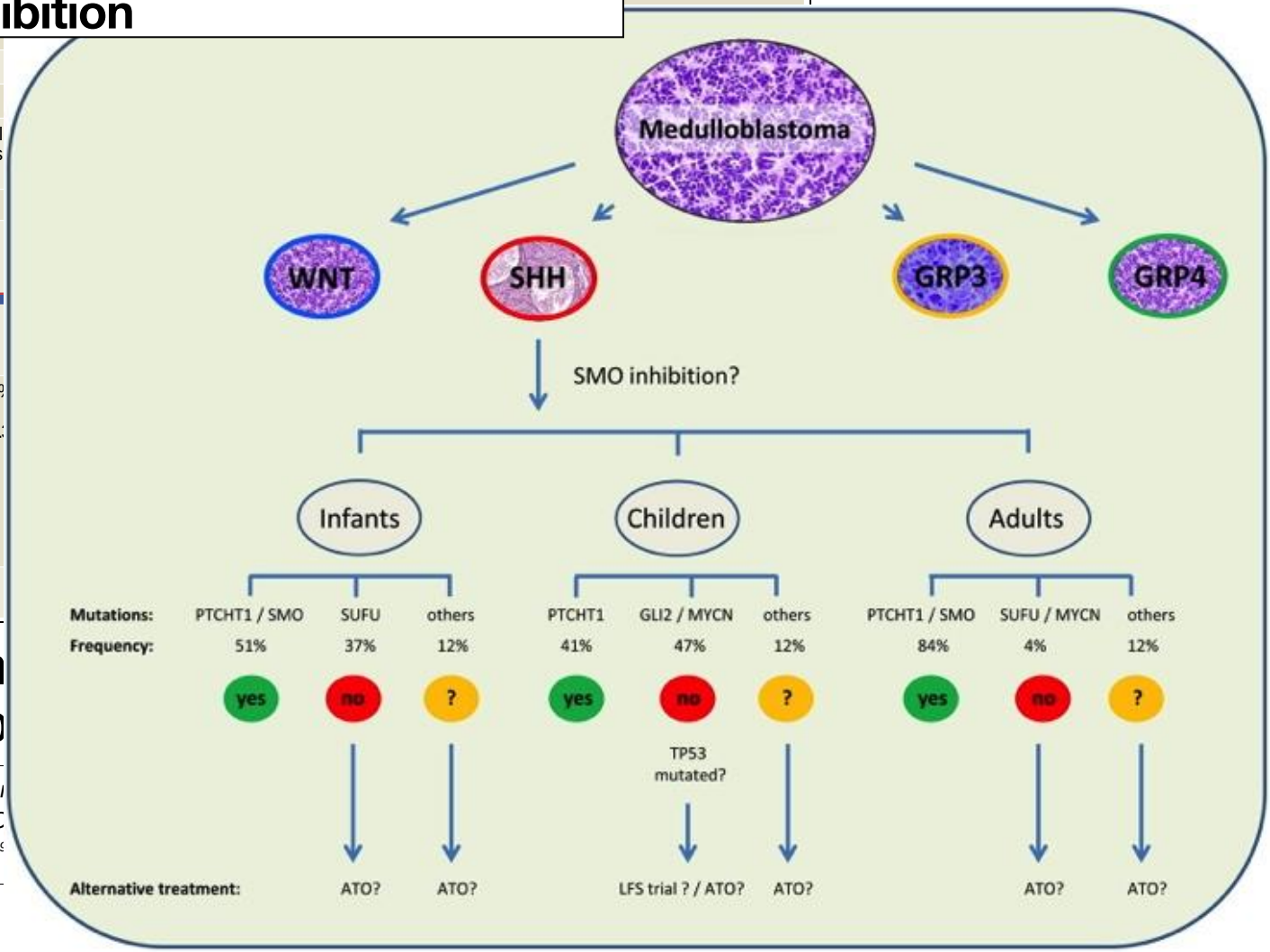
Cancer Cell
Article

Cancer Cell *25*, 393–405, March 17, 2014

Genome Sequencing of SHH Medulloblastoma Predicts Genotype-Related Response to Smoothened Inhibition



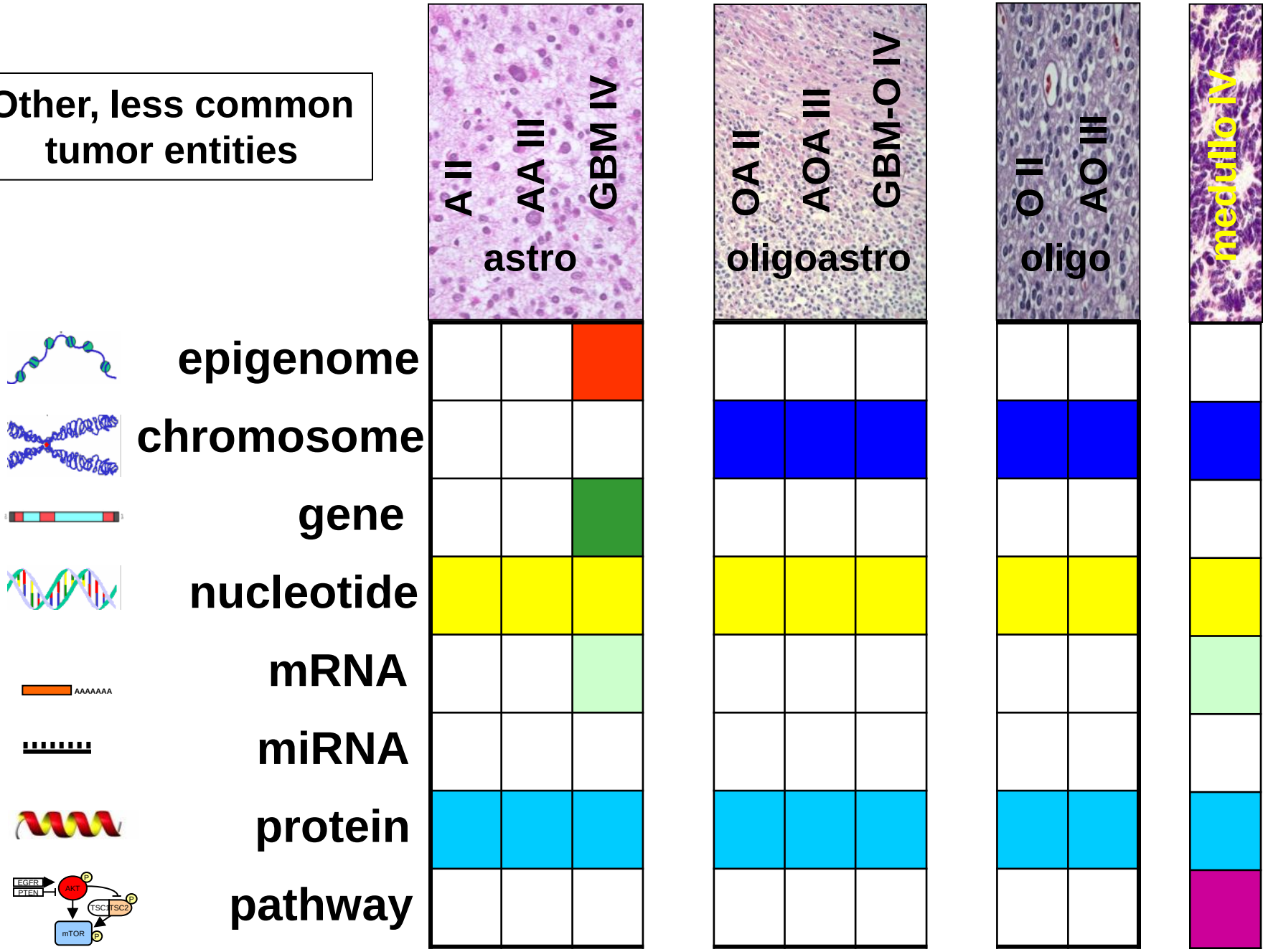
Metastasis at diagnosis	~5–10%
Overall survival (5 years)	~95%
Proposed cell of origin	Lower rhombic l progenitor cells
Genomic features	
Cytogenetics	
Driver genes‡	• *CTNNB1* (90.6% • *DDX3X* (50%) • *SMARCA4* (26.3 • *MLL2* (12.5%) • *TP53* (12.5%)
Expression signature	WNT signalling



Medulloblaston
the end of the b

Paul A. Northcott[1], David T. W. Jo
Richard J. Gilbertson[2], Yoon-Jae C
Peter Lichter[7], Michael D. Taylor[8,9

Other, less common tumor entities



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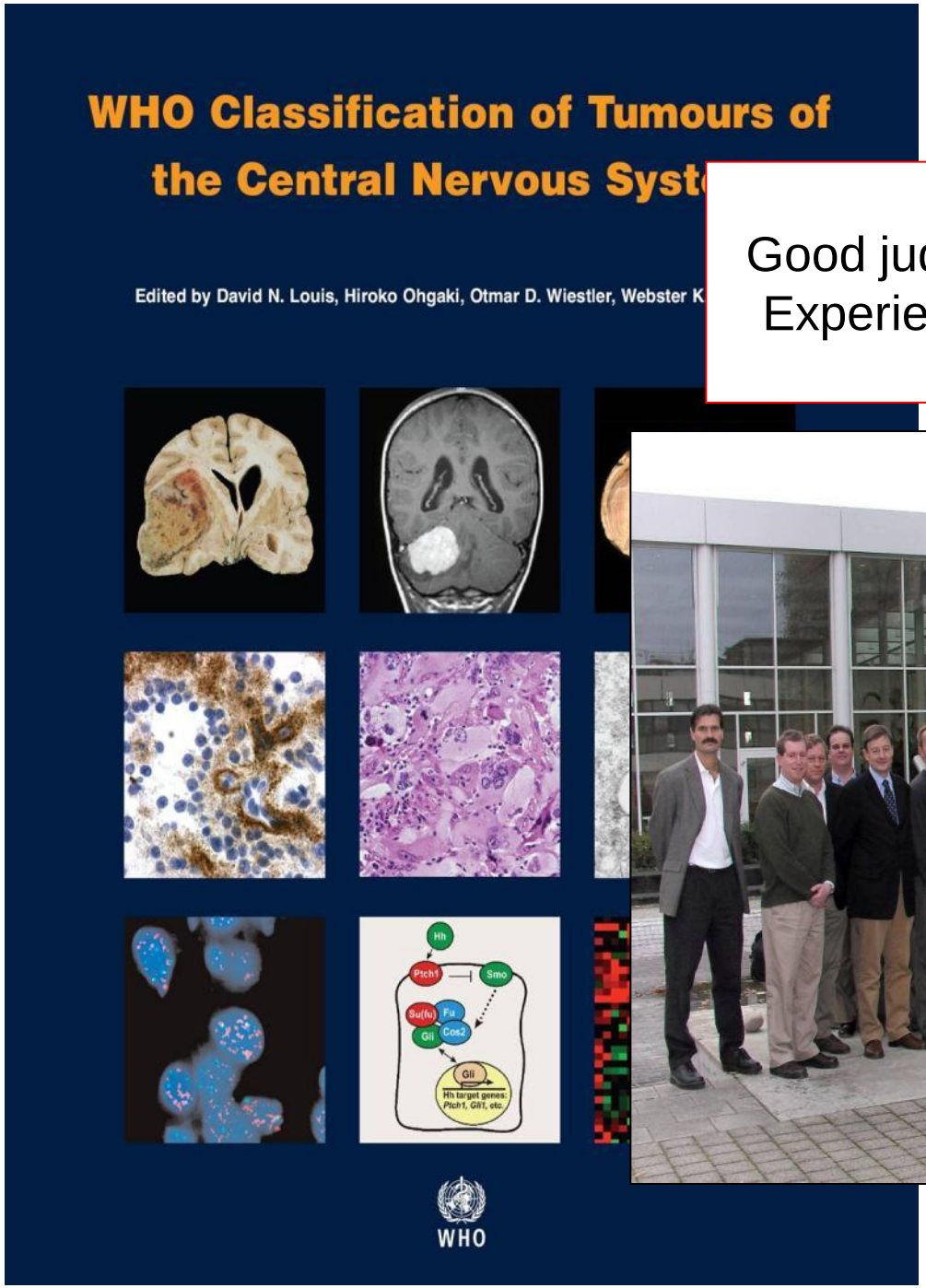
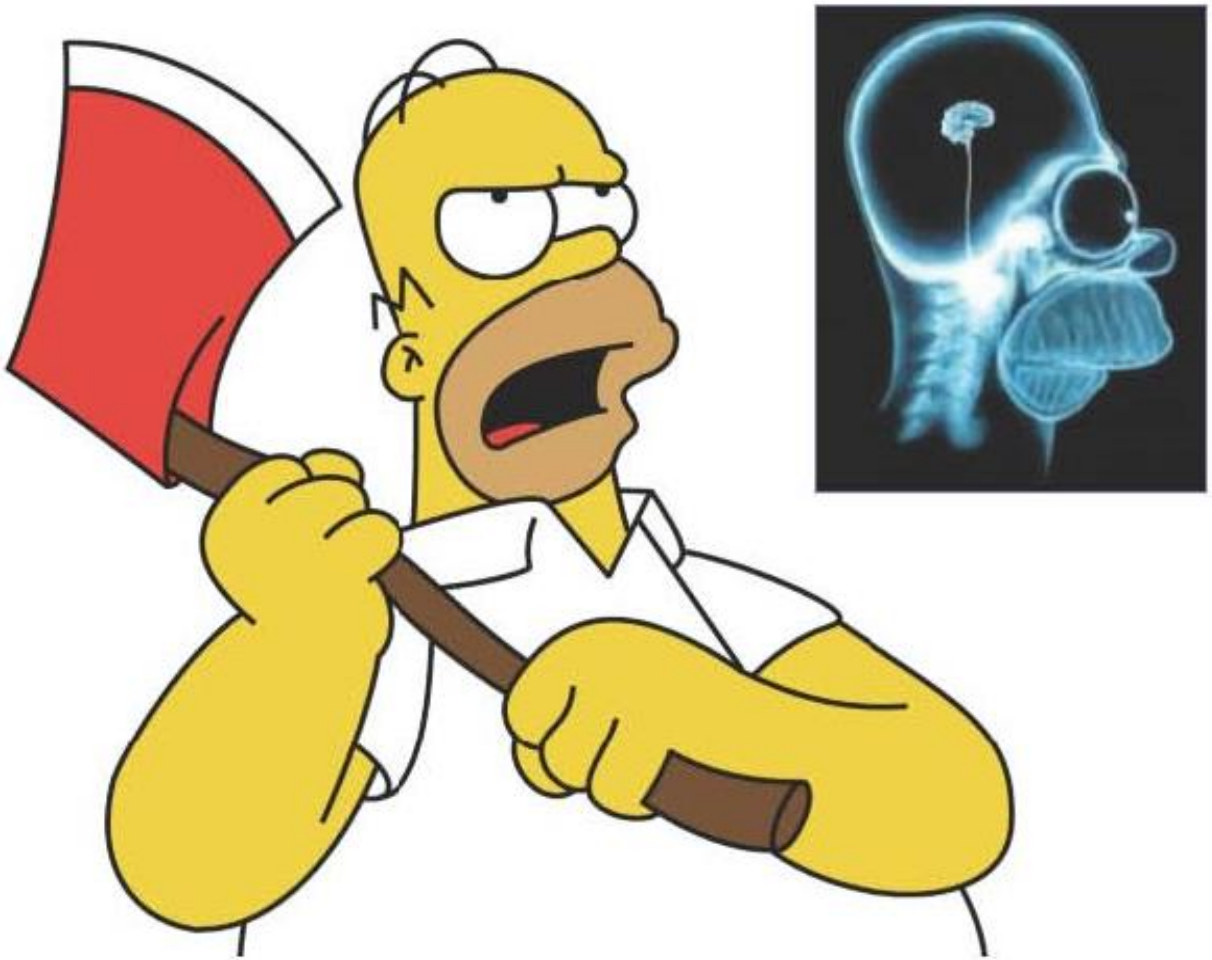
1. Adding more objectivity
2. Incorporating "non-histological" data
3. Grading brain tumors
4. Completion of 4th edition series



Good judgment is the result of experience.
Experience is the result of bad judgment.

A fool with a (molecular) tool is still a fool …



Compliments of Dr. Pieter Wesseling

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Practical challenge: what if techniques are not universally available?

- Do all diagnoses need to be able to be rendered in any area of the globe?
- What is a reasonably practical diagnostic state between the two extremes of *"all diagnoses should be based on H&E"* and *"all diagnoses should be based on deep sequencing"*?

Practical challenge: time vs. technology

- Diagnoses need to be rendered on the order of *days*
- Molecular profiling today requires some *weeks*

Practical challenge: depth of knowledge and relevance varies between tumor types

- 2007 WHO classification of brain tumors has >100 entities
- Not all have known molecular characteristics
- Some known molecular characteristics are not of known diagnostic, prognostic or predictive relevance

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Problem: WHO grading of brain tumors differs from WHO grading of non-CNS tumors

- Most tumor types are graded *within the tumor type*, e.g., “malignant peripheral nerve sheath tumor, grade 1 of 3”
- CNS tumors have a grade *assigned to each tumor type* that correlates with *generalized* biological behavior, e.g., glioblastoma *is* grade IV and pilocytic astrocytoma *is* grade I
- → *This restricts the flexibility of the CNS WHO classification*
- → *This hampers consistent implementation*

A Review of the Collection of WHO Grade for Brain and CNS Tumors in Cancer Registration

QT Ostrom[1,2], C Kruchko[2], JS Barnholtz-Sloan[1,2]

•Case Comprehensive Cancer Center, Case Western Reserve University School of Medicine, Cleveland, OH[1], Central Brain Tumor Registry of the United States, Hinsdale, IL[2],

Results

- Percentages of unknown/missing WHO grade varied greatly by histology with <15% unknown/missing observed for anaplastic oligodendroglioma and oligoastrocytoma/anaplastic oligoastrocytoma (all malignant tumors), and > 80% for craniopharyngioma and hemangioblastoma and > 50% for meningioma (non-malignant tumors).

- Percentages of correctly classified WHO grade varied greatly by tumor histology ranging from 19.8% for craniopharyngioma (non-malignant) to 80.1% for oligoastrocytoma/anaplastic oligoastrocytoma (malignant).

Source: Surveillance, Epidemiology, and End Results (SEER) 18, 2006-2010

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Completion of the 4th edition series

1. Multiple 4th edition blue books remain to be completed
2. WHO/IARC decisions pending on 5th editions
3. As a result, a 5th edition CNS WHO is many years off

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Flexibility of current WHO blue book format

- Dual strengths of current“blue book” series (classification and textbook)

Editions 1 and 2

It will, of course, be appreciated that this classification reflects the present state of knowledge, and modifications are likely to be needed as experience and new knowledge accumulate. *Although the present classification has been adopted by the members, it necessarily represents a view from which some pathologists may wish to dissent. It is nevertheless hoped that, in the interests of international cooperation, all pathologists will try to use the classification as presented…*

The publications in the series International Histological Classification of Tumours are not intended to serve as textbooks but rather to promote the adoption of a uniform terminology that will facilitate and improve communication among cancer workers. For this reason the literature references have intentionally been kept to a minimum and readers should refer to standard works for more complete bibliographies.


THESE ARE THE COMMANDMENTS... THOSE OVER THERE ARE THE GOVERNMENT GUIDELINES THAT GO WITH THEM.

WHO Classification of Tumours of the Nervous System

TUMOURS OF NEUROEPITHELIAL TISSUE

Astrocytic tumours	
Pilocytic astrocytoma	9421/1[1]
Pilomyxoid astrocytoma	*9425/3**
Subependymal giant cell astrocytoma	9384/1
Pleomorphic xanthoastrocytoma	9424/3
Diffuse astrocytoma	9400/3
Fibrillary astrocytoma	9420/3
Gemistocytic astrocytoma	9411/3
Protoplasmic astrocytoma	9410/3
Anaplastic astrocytoma	9401/3
Glioblastoma	9440/3
Giant cell glioblastoma	9441/3
Gliosarcoma	9442/3
Gliomatosis cerebri	9381/3
Oligodendroglial tumours	
Oligodendroglioma	9450/3
Anaplastic oligodendroglioma	9451/3
Oligoastrocytic tumours	
Oligoastrocytoma	9382/3
Anaplastic oligoastrocytoma	9382/3
Ependymal tumours	
Subependymoma	9383/1
Myxopapillary ependymoma	9394/1
Ependymoma	9391/3
Cellular	9391/3
Papillary	9393/3
Clear cell	9391/3
Tanycytic	9391/3
Anaplastic ependymoma	9392/3
Choroid plexus tumours	
Choroid plexus papilloma	9390/0
Atypical choroid plexus papilloma	*9390/1**
Choroid plexus carcinoma	9390/3
Other neuroepithelial tumours	
Astroblastoma	9430/3
Chordoid glioma of the third ventricle	9444/1
Angiocentric glioma	*9431/1**
Neuronal and mixed neuronal-glial tumours	
Dysplastic gangliocytoma of cerebellum (Lhermitte-Duclos)	9493/0
Desmoplastic infantile astrocytoma/ ganglioglioma	9412/1
Dysembryoplastic neuroepithelial tumour	9413/0
Gangliocytoma	9492/0
Ganglioglioma	9505/1
Anaplastic ganglioglioma	9505/3
Central neurocytoma	9506/1
Extraventricular neurocytoma	*9506/1**
Cerebellar liponeurocytoma	*9506/1**
Papillary glioneuronal tumour	*9509/1**
Rosette-forming glioneuronal tumour of the fourth ventricle	*9509/1**
Paraganglioma	8680/1
Tumours of the pineal region	
Pineocytoma	9361/1
Pineal parenchymal tumour of intermediate differentiation	9362/3
Pineoblastoma	9362/3
Papillary tumour of the pineal region	*9395/3**
Embryonal tumours	
Medulloblastoma	9470/3
Desmoplastic/nodular medulloblastoma	9471/3
Medulloblastoma with extensive nodularity	*9471/3**
Anaplastic medulloblastoma	*9474/3**
Large cell medulloblastoma	9474/3
CNS primitive neuroectodermal tumour	9473/3
CNS neuroblastoma	9500/3
CNS ganglioneuroblastoma	9490/3
Medulloepithelioma	9501/3
Ependymoblastoma	9392/3
Atypical teratoid / rhabdoid tumour	9508/3

TUMOURS OF CRANIAL AND PARASPINAL NERVES

Schwannoma (neurilemoma, neurinoma)	9560/0
Cellular	9560/0
Plexiform	9560/0
Melanotic	9560/0
Neurofibroma	9540/0
Plexiform	9550/0
Perineurioma	
Perineurioma, NOS	9571/0
Malignant perineurioma	9571/3
Malignant peripheral nerve sheath tumour (MPNST)	
Epithelioid MPNST	9540/3
MPNST with mesenchymal differentiation	9540/3
Melanotic MPNST	9540/3
MPNST with glandular differentiation	9540/3

TUMOURS OF THE MENINGES

Tumours of meningothelial cells	
Meningioma	9530/0
Meningothelial	9531/0
Fibrous (fibroblastic)	9532/0
Transitional (mixed)	9537/0
Psammomatous	9533/0
Angiomatous	9534/0
Microcystic	9530/0
Secretory	9530/0
Lymphoplasmacyte-rich	9530/0
Metaplastic	9530/0
Chordoid	9538/1
Clear cell	9538/1
Atypical	9539/1
Papillary	9538/3
Rhabdoid	9538/3
Anaplastic (malignant)	9530/3
Mesenchymal tumours	
Lipoma	8850/0
Angiolipoma	8861/0
Hibernoma	8880/0
Liposarcoma	8850/3
Solitary fibrous tumour	8815/0
Fibrosarcoma	8810/3
Malignant fibrous histiocytoma	8830/3
Leiomyoma	8890/0
Leiomyosarcoma	8890/3
Rhabdomyoma	8900/0
Rhabdomyosarcoma	8900/3
Chondroma	9220/0
Chondrosarcoma	9220/3
Osteoma	9180/0
Osteosarcoma	9180/3
Osteochondroma	9210/0
Haemangioma	9120/0
Epithelioid haemangioendothelioma	9133/1
Haemangiopericytoma	9150/1
Anaplastic haemangiopericytoma	9150/3
Angiosarcoma	9120/3
Kaposi sarcoma	9140/3
Ewing sarcoma - PNET	9364/3
Primary melanocytic lesions	
Diffuse melanocytosis	8728/0
Melanocytoma	8728/1
Malignant melanoma	8720/3
Meningeal melanomatosis	8728/3
Other neoplasms related to the meninges	
Haemangioblastoma	9161/1

LYMPHOMAS AND HAEMATOPOIETIC NEOPLASMS

Malignant lymphomas	9590/3
Plasmacytoma	9731/3
Granulocytic sarcoma	9930/3

GERM CELL TUMOURS

Germinoma	9064/3
Embryonal carcinoma	9070/3
Yolk sac tumour	9071/3
Choriocarcinoma	9100/3
Teratoma	9080/1
Mature	9080/0
Immature	9080/3
Teratoma with malignant transformation	9084/3
Mixed germ cell tumour	9085/3

TUMOURS OF THE SELLAR REGION

Craniopharyngioma	9350/1
Adamantinomatous	9351/1
Papillary	9352/1
Granular cell tumour	9582/0
Pituicytoma	*9432/1**
Spindle cell oncocytoma of the adenohypophysis	*8291/0**

METASTATIC TUMOURS

[1] Morphology code of the International Classification of Diseases for Oncology (ICD-O) (614A) and the Systematized Nomenclature of Medicine (http://snomed.org). Behaviour is coded /0 for benign tumours, /3 for malignant tumours and /1 for borderline or uncertain behaviour.

* The italicised numbers are provisional codes proposed for the 4th edition of ICD-O. While they are expected to be incorporated into the next ICD-O edition, they currently remain subject to change.

Pineal tumor examples

1979

D. PINEAL CELL TUMOURS

1. *Pineocytoma* [*pinealocytoma*] (Fig. 36): An uncommon tumour composed of pineal cells. Their polar processes often radiate toward the vascular stroma (specific silver impregnations for pineal parenchymal cells may demonstrate the typical cell processes with club-like expansions at their tips, as described by Rio-Hortega).

Histologically the pineocytoma may correspond to grades I to III. This lack of precision results from the lack of information concerning the behaviour of these growths.

2. *Pineoblastoma* [*pinealoblastoma*] (Fig. 37): A rare, pineal tumour consisting of small, poorly differentiat cytological features and architecture resemble tho blastoma. This tumour corresponds to grade IV.

2000

Pineoblastoma

H. Mena
Y. Nakazato
A. Jouvet
B.W. Scheithauer

Definition
A highly malignant, primitive embryonal tumour of the pineal gland with preferential manifestation in children, composed of patternless sheets of densely packed small cells with round-to-irregular nuclei and scant cytoplasm.

ICD-O code: 9362/3

Grading
Pineoblastomas correspond histologically to WHO grade IV.

Incidence, age and sex distribution
Pineoblastomas are rare intracranial tumors that constitute approximately 45% of all pineal parenchymal tumours. They can arise at any age, but usually occur in the first two decades of life with a predilection for children [223, 582, 604, 992, 1361]. There is a slight male preponderance (Fig. 7.1).

Clinical features
Symptoms and signs
The clinical presentation of pineoblastoma is similar to that of other tumours of the pineal region (see pineocytoma). The interval between initial symptoms and surgery may be as short as one month or less [148, 223, 671]. Median post-surgical survivals vary from 24 to 30 months [223, 582, 992].

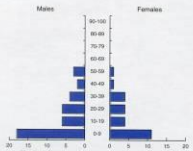


Fig. 7.1 Age and sex distribution of pineoblastoma, based on 64 published cases.

Neuroimaging
In contrast to pineocytoma, the CT appearance of pineoblastoma is that of a large, lobulated or poorly demarcated, homogeneous mass, which is hyperdense after contrast enhancement. Calcification is infrequent. On T1-weighted MRI scan, pineoblastomas are hypo-to-isointense, but are heterogeneous upon contrast administration [231, 356].

Macroscopy
Pineoblastomas are soft, friable and poorly demarcated [148]. Haemorrhage and/or necrosis may be present, but calcification is rare. Infiltration of surrounding structures, including the meninges is common. The same is true of craniospinal dissemination [148, 223, 326, 356, 582, 604, 671, 992, 1546].

Histopathology
Constituting the most primitive of pineal parenchymal tumours, pineoblastomas are composed of patternless sheets of densely packed small cells with round-to-irregular nuclei and scant cytoplasm. Pineocytomatous rosettes are lacking, but Homer-Wright and Flexner-Wintersteiner rosettes may be seen.
Pineoblastomas are highly cellular neoplasms resembling other small cell, embryonal and primitive neuroectodermal tumours of the CNS. Primitive in appearance, the cells have a high nuclear cytoplasmic ratio, round-to-irregular, hyperchromatic nuclei with occasional, small, single nucleoli, scant cytoplasm, and indistinct cell borders. The cells are arranged in a diffuse pattern, interrupted only by the occasional formation of Homer-Wright or Flexner-Wintersteiner rosettes. The latter indicating retinoblastic differentiation as do fleurettes. Rarely a papillary pattern may be seen. Necrosis is common, but mitotic activity varies considerably, and may be accompanied by microcalcifications. Silver stains for pineal parenchymal cells demonstrate scant cytoplasm and few cellular processes [1881]. Mela-

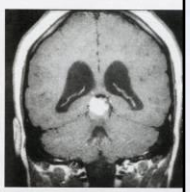


Fig. 7.2 On T1-weighted MRI, pineoblastoma show homogeneous contrast enhancement.

nin production, cartilaginous and rhabdo myoblastic differentiation may be presen in rare pineoblastomas, such tumors ar referred as pineal anlage tumors [582 1089, 976]. Occasionally, pineoblastoma

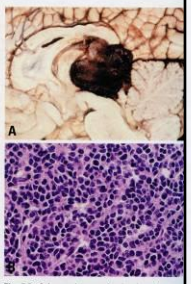


Fig. 7.3 A Large, haemorrhagic pineoblastoma B Highly cellular pineoblastoma showing undifferentiated small cell histology.

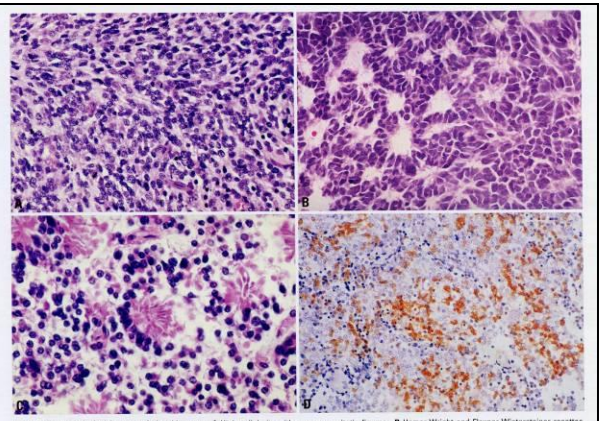


Fig. 7.4 Histopathological features of pineoblastoma. A High cellularity with numerous mitotic figures. B Homer-Wright and Flexner-Wintersteiner rosettes. C Fleurettes. D Focal expression of retinal S-antigen.

may exhibit a biphasic pattern, with alternating areas resembling pineocytoma and pineoblastoma.

Immunohistochemistry
The immunophenotype of pineoblastomas in terms of neuronal, glial and photoreceptor markers is similar to that of pineocytomas. Reactivity is variable, but include positivity for synaptophysin, NSE, NFP, class III beta-tubulin, chromogranin A, and retinal S- antigen [992, 1089, 1167]. Reactivity for beta-crystallin, GFAP and desmin has been reported on rare occasions; in such instances, every effort should be made to exclude the presence of entrapped reactive astrocytes.

Electron microscopy
Characterized by a relative lack of significant differentiation, the fine structure of pineoblastoma is similar to that of any poorly differentiated neuroectodermal neoplasm. Cells have round-to-oval, or slightly irregular nuclei and abundant euchromatin as well as heterochromatin. Cytoplasm is scant and contains polyribosomes, few profiles of rough endoplasmic reticulum, small mitochondria, as well as occasional microtubules, intermediate filaments, and lysosomes [965, 1013, 1089]. Dense core granules are rarely seen in the cell body [965, 1013]. Cell processes, poorly formed and short, may contain microtubules as well as scant dense core granules [965]. Bulbous endings are not identified [1013]. Junctional complexes of zonula adherens and zonula occludens type may be present between cells and processes [717, 965, 1013, 1089]. Synapses are absent [1089]. Cilia with a 9+0 microtubular pattern are occasionally seen [965]. Rarely, cells radially arranged around a small central lumen may be encountered [1089].

Genetic susceptibility
Primitive neuroepithelial tumours of the pineal region having a pineoblastomatous appearance may be seen in patients with familial (bilateral) retinoblastoma, an occurrence termed "trilateral retinoblastoma syndrome" [319, 928] and have also been reported in a patient with familial adenomatous polyposis [1884].

Genetics
Few studies deal with the cytogenetic aberrations of pineoblastoma. Chromosomal analysis of cultured cells from a pineoblastoma showed an interstitial deletion of the long arm of chromosome 11, del(11) (q13.1q13.5) [1888]. In vitro, the pineoblastoma cell line PER-480 showed evidence of neuronal differentiation and two karyotype abnormalities, a der XXX (10)((10;17) and a der XXX (16) t (1;16), as well as enhanced expression but not amplification of a member of the MYC family of

Differences between editions 1 and 2 versus editions 3 and 4

- Editions 1 and 2:
  - Pure definitional classification systems
- Editions 3 and 4
  - Definitional classification system (chart)
  - Textbook

Problem: the needs and process of updating a classification system differ from those of a textbook
Opportunity: the textbook component allows greater flexibility

Outline

- Background on WHO classifications
- Challenges and opportunities for the next WHO classification of nervous system tumors
  - How “periodic” should “periodic” be?
  - How narrowly should entities be defined and by what approaches should entities be defined?
  - What are the limitations and idiosyncrasies of the current system?
  - What are the flexibilities of the current system?

Outline

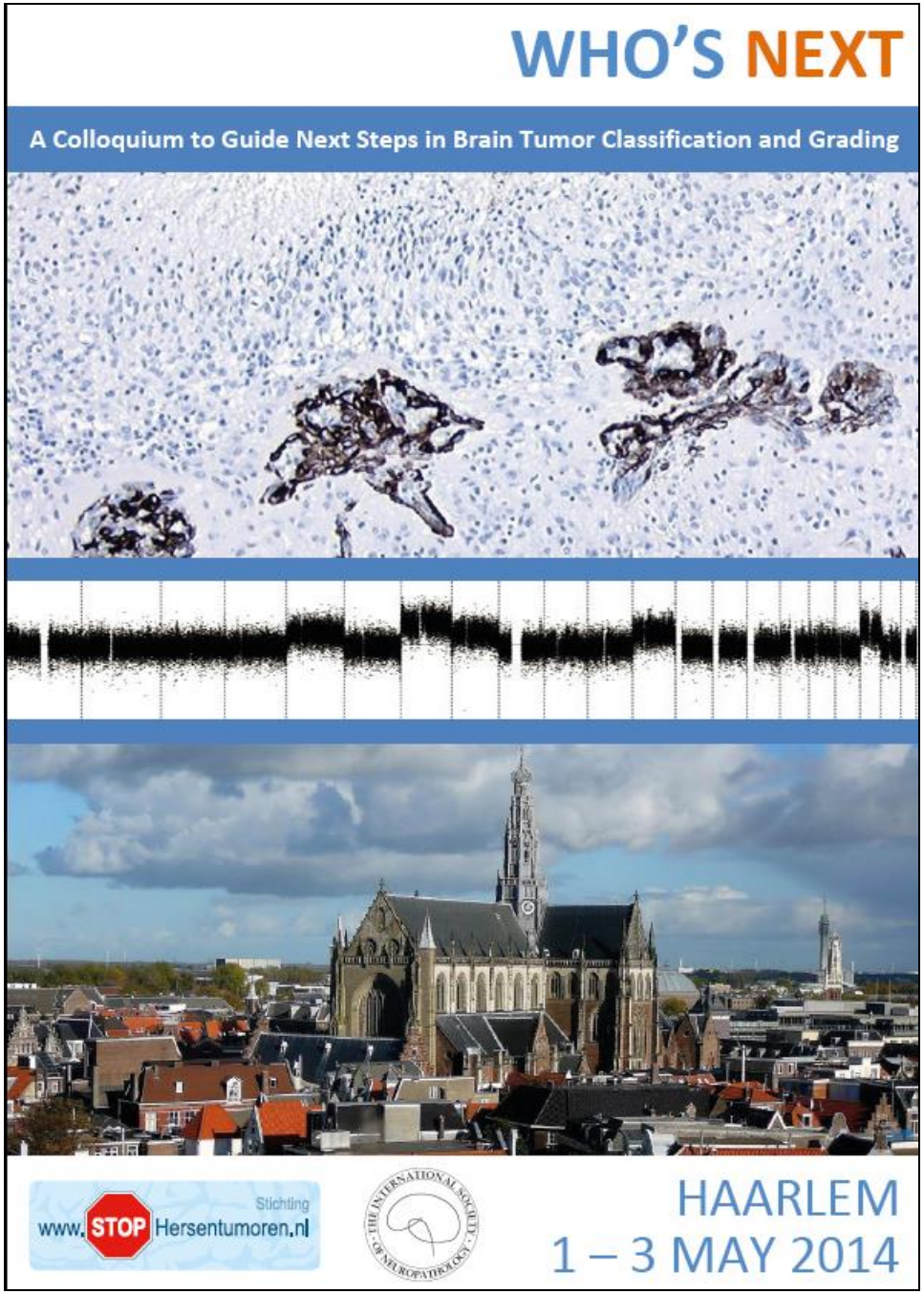
- Background on WHO classifications
- Challenges and opportunities for the next WHO classification of nervous system tumors
- The Haarlem meeting and its recommendations
- Next steps for the forthcoming WHO update and a glimpse at future classification systems

Problem: the shifting basis for classification

- Insights into the molecular basis of human tumors have radically changed both our biological understanding of neoplasms as well as our abilities to diagnose tumors and estimate their prognosis and likelihood of response to specific therapies
- Therefore, a critical scientific question has arisen with major practical consequences: *how should molecular information change brain tumor classification*?

First step to address challenges

- Address underlying scientific principles rather than in terms of individual tumor entities
  - 2007 WHO classification of brain tumors has >100 entities
  - Not all have known molecular or diagnostically relevant characteristics
  - The basic questions underlying those that do have known molecular characteristics are similar



"WHO's Next?"

A Colloquium to Guide Next Steps in Brain Tumor Classification and Grading

Sponsored by the International Society of Neuropathology

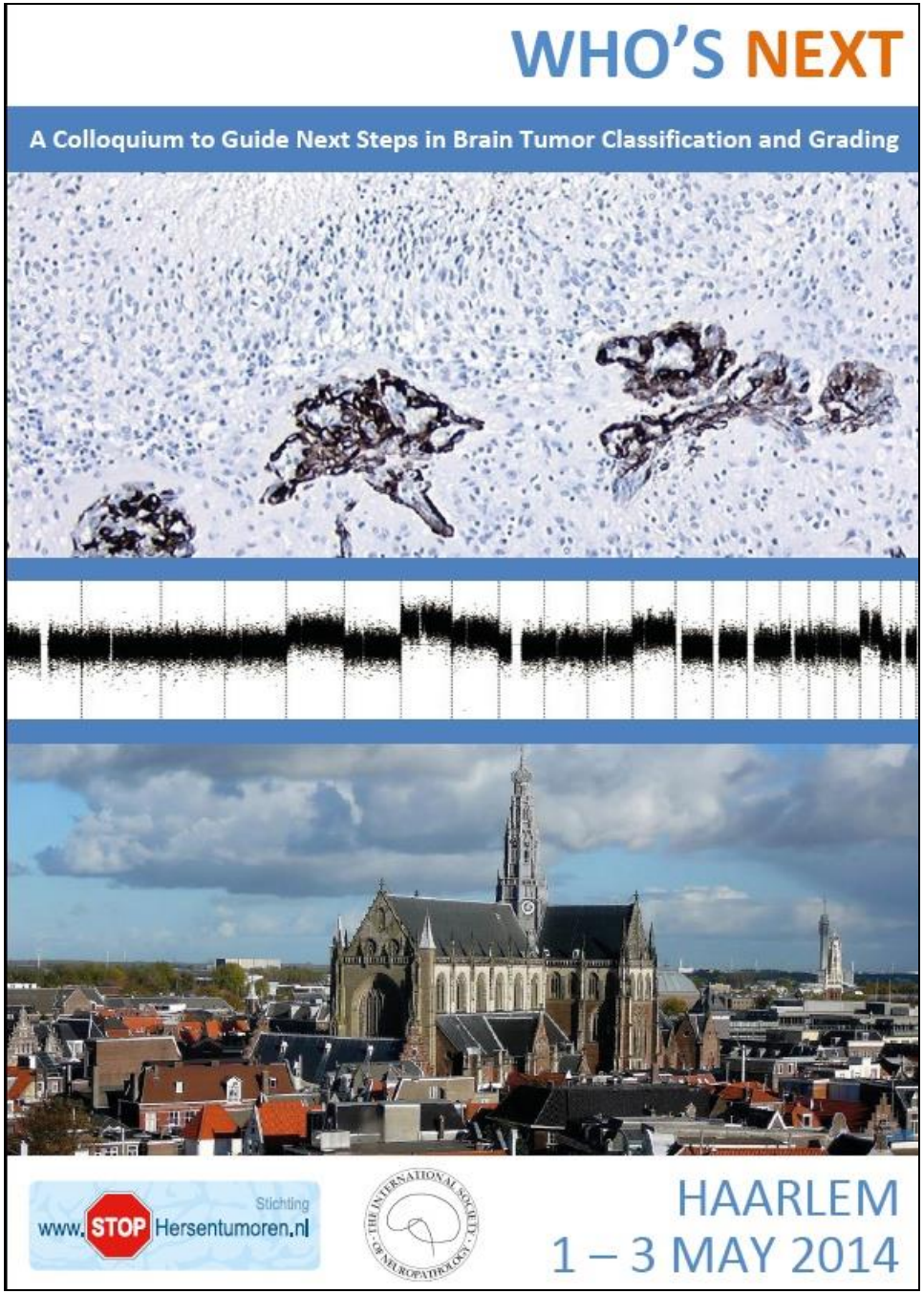
Made possible through generous support from the STOPbraintumors Foundation

Organizers:

- ***David Louis***
- ***Pieter Wesseling***
- ***Arie Perry***

Program Committee:

- ***Peter Burger***
- ***David Ellison***
- ***Guido Reifenberger***
- ***Andreas von Deimling***



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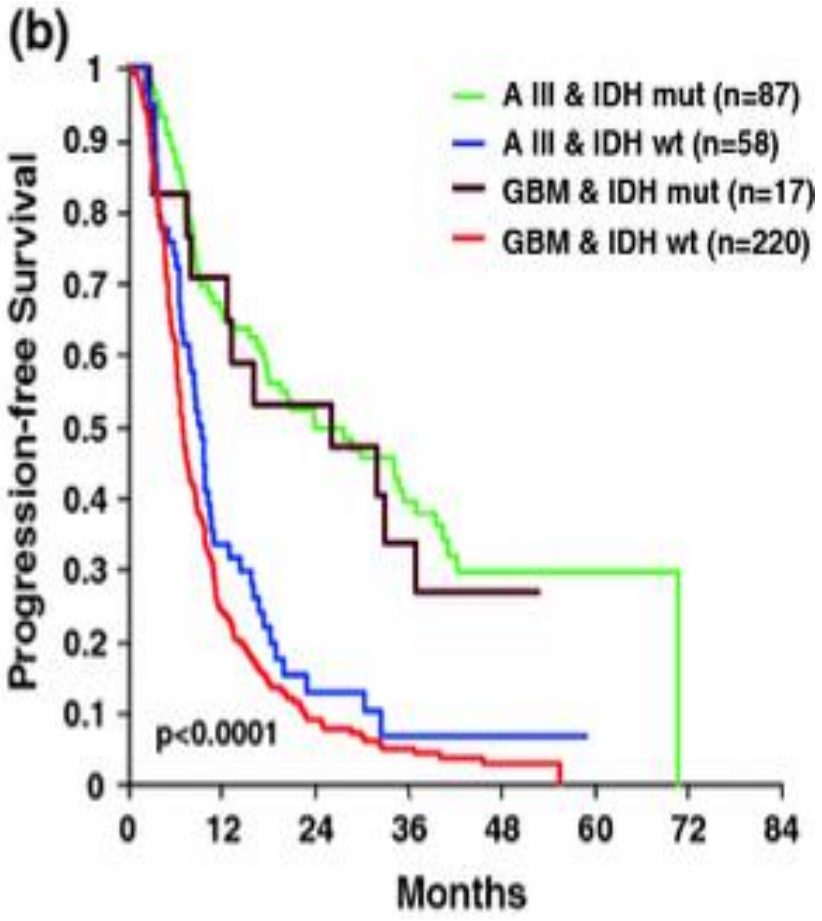
Pieter Wesseling
Otmar Wiestler

Example



Hartmann et al., Acta Neuropathologica 2010

Should a histological glioblastoma with an IDH mutation be termed:

- Glioblastoma, grade IV, IDH mutant?
- Glioblastoma, IDH mutant
- Anaplastic astrocytoma?
- Glioblastoma, grade III?

Major question:

How can non-histological criteria (e.g., molecular, imaging, clinical, other?) be used to enhance typing and grading of human brain tumors?

Subquestions:

1. What is the relationship between diagnosis and grade? Can tumor type and tumor grade be separated from one another, as occurs in other (non-brain) tumor types? This also brings up the question of whether grade reflects natural history or likely prognosis after therapy.
2. How does one make recommendations about the use of molecular testing? Is molecular analysis required or optional? If optional, how does one formulate diagnoses to demonstrate this variability clearly (see “straw man” below*)? If required, does molecular diagnosis become incorporated into overall diagnosis, or be added as an extra level to the histological diagnosis (see * below)? Does one make recommendations about the type of test to use? Does one make recommendations about specific cut-off levels?
3. How does one formulate diagnoses if some institutions use molecular tests and others do not? If one uses molecular parameters to classify tumors, what does one call tumors that have the histological appearance but not the defining molecular feature? And what what does one do with a tumor that has the defining molecular features of one tumor type, but the histologic appearance of another? In the era of broad sequencing/profiling, how does one classify a tumor with an unexpected but diagnostic mutation/profile?
4. Should we recommend the use of radiology and clinical parameters for typing and grading—keeping in mind that we already occasionally use such features for classification (e.g., location to diagnose medulloblastoma)?

Simplified goal/question

How will we structure reports that include non-histological data?

Background of thinking of the WHO classification for lymphoma

There is no single parameter as gold standard for a class, but the balance between the 4 parameters may vary per disease

Ideally a "disease entity" is defined by specific biological understanding → target for treatment

Compliments of Dr. Daphne de Jong

fundamental decision in WHO hematopathology

- entities should be narrowly defined, contamination should be avoided, no wastebaskets
- Better throw cases out than contaminate
- Descriptive "classes" to isolate cases with features overlapping between entities for further study and discussion

How to deal with things that do not fit in?

- Hematopathology has chosen not to force outliers into existing entities
- Accept insufficient knowledge and set aside for better times
  - Aggressive B-cell lymphoma with features intermediate between cHL and DLBCL
  - Aggressive B-cell lymphoma with features intermediate between BL and DLBCL

Compliments of Dr. Daphne de Jong


Pint Cove
Intervale S Rd
Shore Rd
Pequanic Rd
Anbewold Ln
Cape Neddick Campground
Lawrie Ave
Shore Rd
Cape Neddick Harbor
Yale Ave
Main St
Bay Haven Rd
Ray Ave
Bay Haven Rd
Hotel Ave
Map
Traffic
Live traffic change
Slow
Fast
200 m
Newport Ave
Imagery ©2014 Cnes/Spot Image, DigitalGlobe, Maine GeoLibrary, USDA Farm Service Agency, Map data ©2014 Google
Edit in Google Map Maker
Report a problem

FIGURE 1-2: An Information Commons might use a Geographic Information System (GIS)-type structure

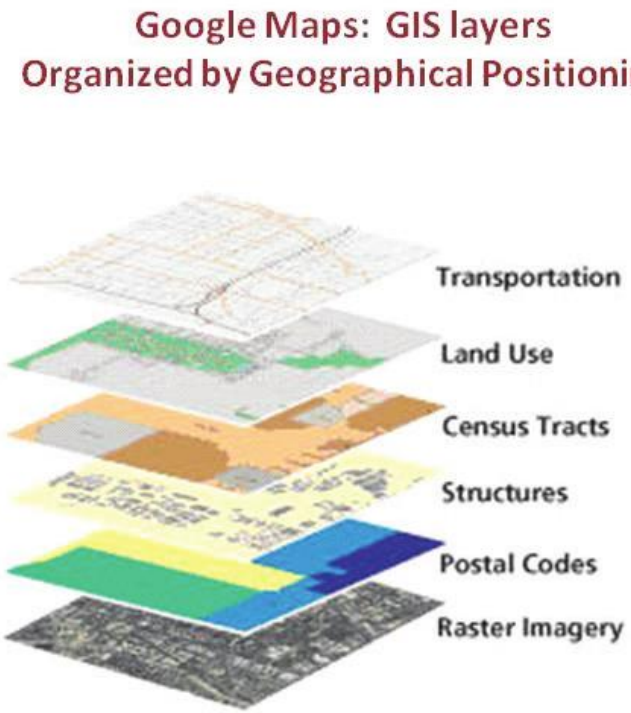
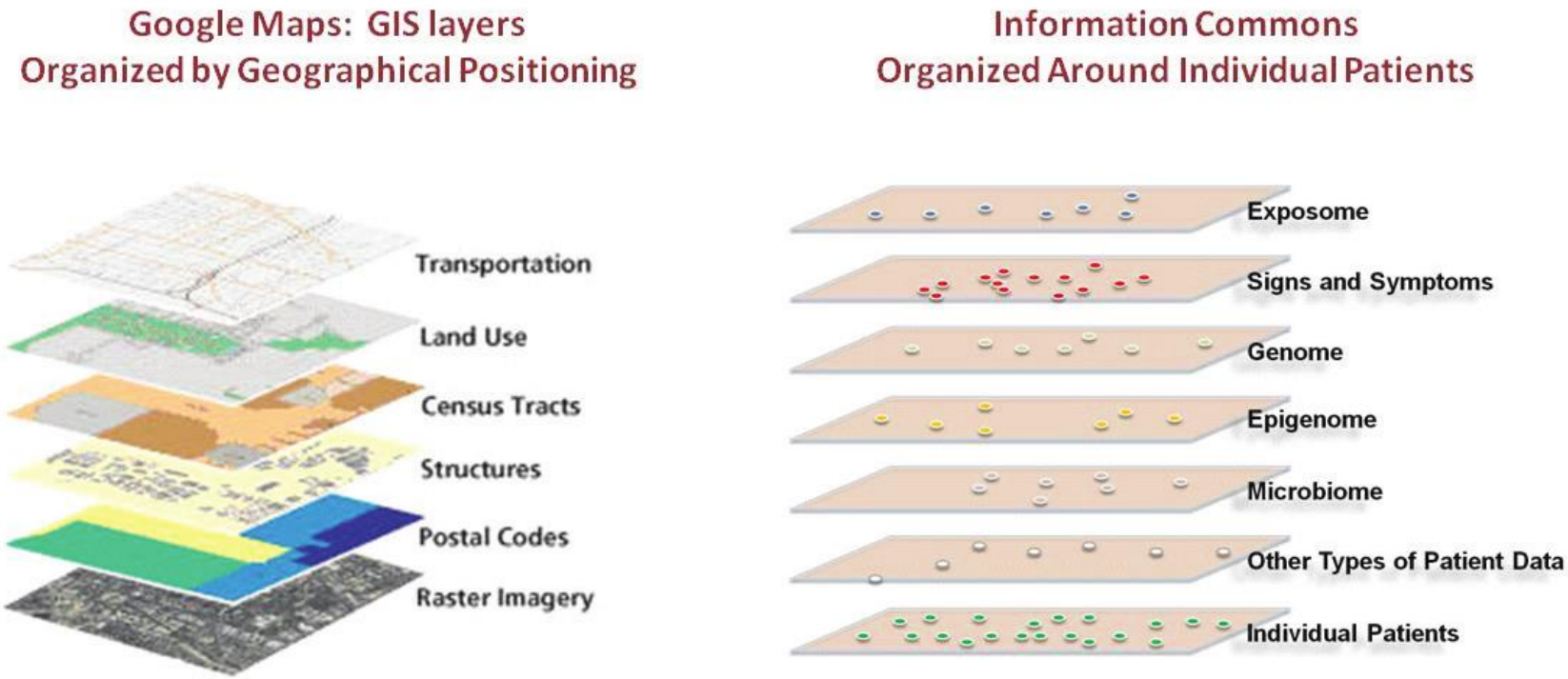


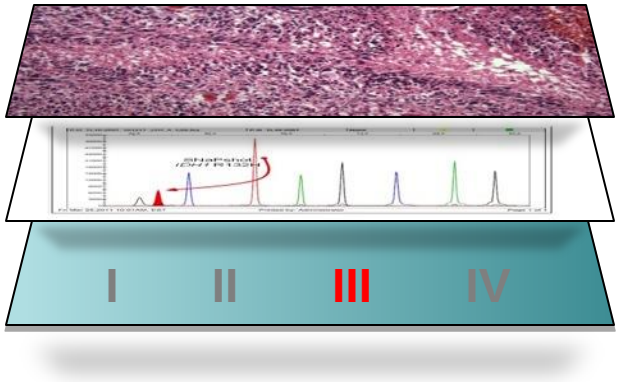
FIGURE 1-2: An Information Commons might use a Geographic Information System (GIS)-type structure



Straw man proposals

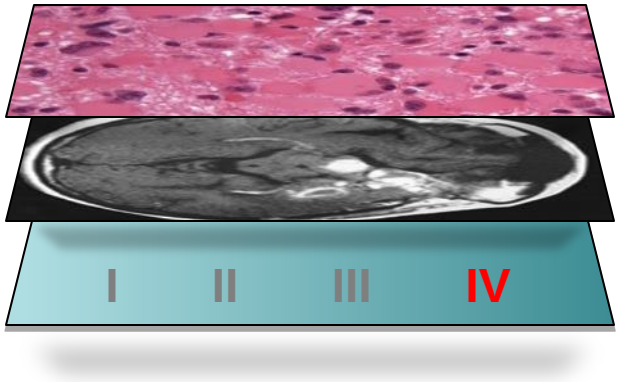
Diagnoses can have three “tiers”:

- Histological: Glioblastoma
- *Molecular*: IDH mutant
- Grade: WHO grade III



Diagnoses can have three “tiers”:

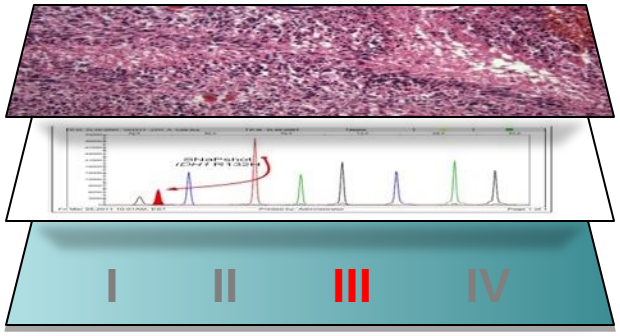
- Histological: Anaplastic astrocytoma
- *Imaging*: Ring-enhancing
- Grade: WHO grade IV



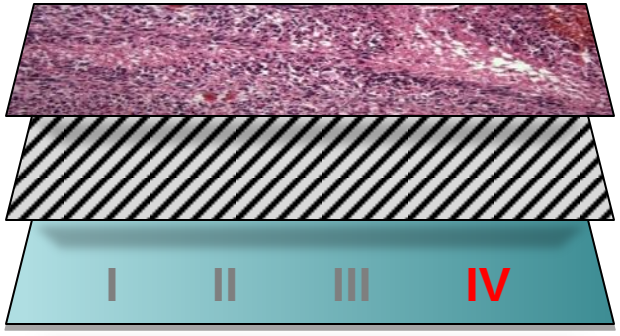
Straw man proposals

Diagnoses can have missing “tiers”:

- Histological: Glioblastoma
- *Molecular*: IDH mutant
- Grade: WHO grade III



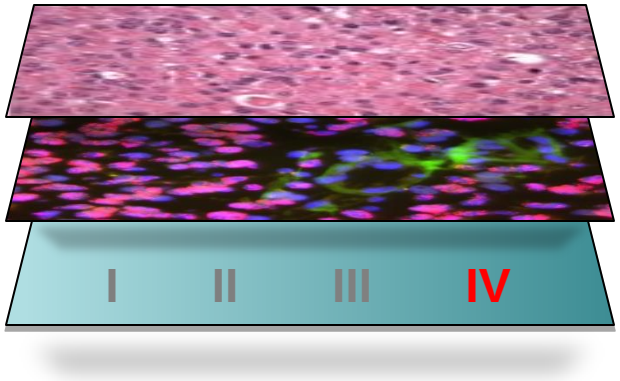
- Histological: Glioblastoma
- *Molecular*: *Not performed*
- Grade: WHO grade IV



Straw man proposals

What if histology is more generic?

- Histological: Glioma
- Molecular: EGFR amp
- Grade: WHO grade IV



from Greg Fuller

TABLE 40–2 Illustrative Molecular Diagnosis Format for Diffuse Glioma (MD Anderson Cancer Center Format)

Diffuse Glioma

IDH status: IDH1 (R132H) mutation present

1p/19q status: codeletion present

Mitotic index (PHH3): 1/1,000

Ki-67 index (MIB1): 3%

(see comment)

Comment

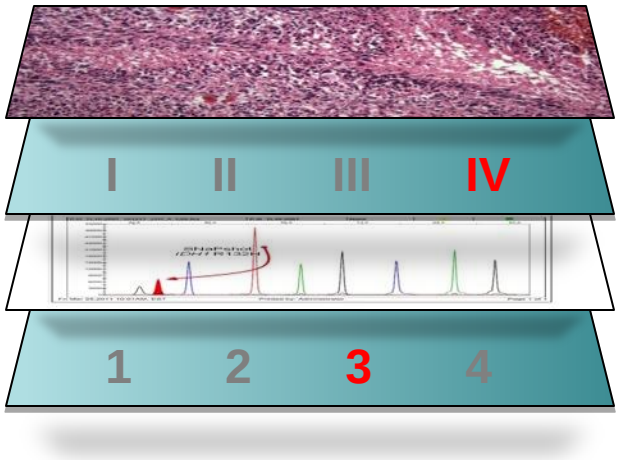
Examination of H&E-stained sections shows a diffuse glioma with morphological features corresponding to oligodendroglioma, grade II, of the WHO classification system. IDH1 (R132H) mutation is determined by immunohistochemistry. 1p/19q deletion status is determined by fluorescence in situ hybridization (FISH) assay. Mitotic index of 1 mitosis per 1000 cells is determined by automated quantitation of phosphohistone H3 (PHH3) immunostain. Ki-67 antigen index of 3% is determined by automated quantitation of MIB-1 immunostain.

Olar, Fuller. In: Principles of Molecular Diagnostics and Personalized Cancer Medicine, 2012

Straw man proposal

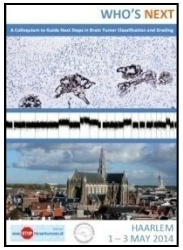
What if there are two kinds of grades,
"histological" and "biological"?

- Histological: Glioblastoma
- Histological Grade: WHO grade IV
- Molecular: IDH mutant
- "Biological" Grade: 3



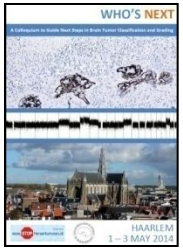
"Biological"?
"Current biological"?
"Current clinico-biological"?

ISN-Haarlem conclusions (1)



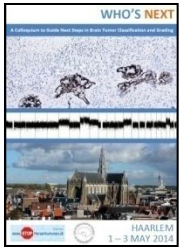
- Molecular information will be incorporated into the definitions of some diagnostic entities
  - For some of these entities, molecular information will be necessary to provide an “integrated” diagnosis and only a descriptive histological diagnosis will be possible if no molecular diagnostic testing is available
  - For other of these entities, molecular information will be necessary to provide an “integrated” diagnosis but a formal “NOS” entity will be available if no molecular diagnostic testing is available
  - To do the above, some disease entities need to be redefined and some new disease entities need to be defined/added
- For some diagnostic entities, histology will remain the basis for definition and diagnosis

ISN-Haarlem conclusions (2)



- Molecular testing and reporting
  - Certain molecular tests will be required, recommended or suggested in order to make diagnoses and/or to guide therapeutic choices; the importance of performing these tests may differ depending on whether they are diagnostic, prognostic and/or predictive
  - Future decisions to incorporate such testing into diagnostic definitions will be based on substantial evidence
  - For some genetic tests, some general approaches may be recommended over others (e.g., detecting whole-arm loss in oligos) as well as second-level tests to follow first-level tests
  - In settings in which molecular testing is recommended or suggested, a report should state if it was not done (“unknown”) or if ordered, along with a reason (e.g., TIFD)
  - Test methodological and results parameters should be indicated in reports
  - Molecular testing must be based on histologically representative tissue

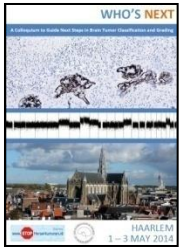
ISN-Haarlem conclusions (3)



- Grade will reflect natural history and will be based on histological findings; for some entities, *avoiding* a histological grade may be preferable

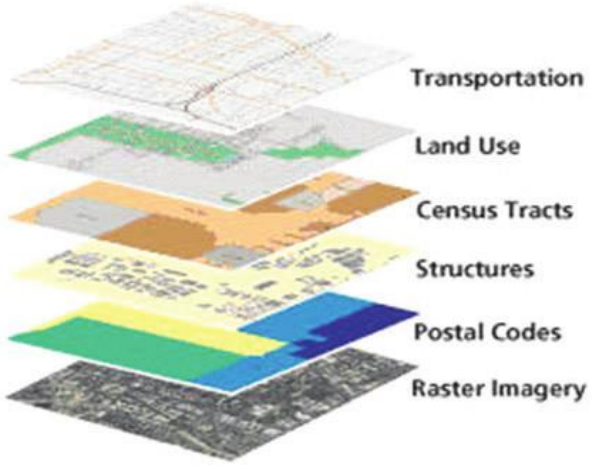
- Some pediatric tumor types will require the creation of entities independent of their adult histological “look-alikes”

ISN-Haarlem format of “layered diagnoses”

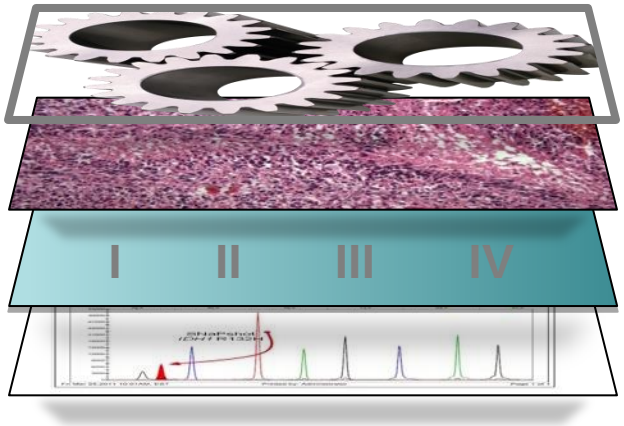


- Integrated Diagnosis (incorporated all aspects of tissue diagnosis)
- Histological Diagnosis
- WHO Grade (histological grade)
- Molecular information

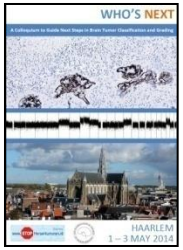
Google Maps: GIS layers
Organized by Geographical Positioning



ISN-Haarlem
layered diagnosis format

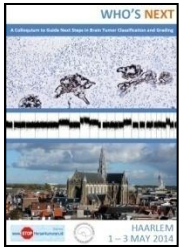


Proposal for the diagnosis of ATRT



- One cannot make the diagnosis of ATRT without INI1 or BRG1 testing
- The diagnosis of ATRT requires both typical pathological features and either INI1 or BRG1 loss
- Tumors that have typical pathological features of ATRT but no IN11 or BRG1 loss might be termed “embryonal tumor with rhabdoid features”
- A laboratory that does not have INI1 and BRG1 immunohistochemistry needs to send the case to another lab for testing

ATRT (1)



Integrated diagnosis:

Histological diagnosis:

Embryonal tumor with rhabdoid features

Histological grade:

Grade IV

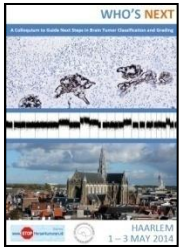
Molecular information:

INI1 absent, BRG1 retained

INI1 retained, BRG1 absent

(Additional information : age, location)

ATRT (2)



Integrated diagnosis:

Histological diagnosis:

Embryonal tumor with rhabdoid features

Histological grade:

Grade IV

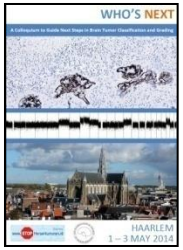
Molecular information:

INI1 retained, BRG1 retained

Not done

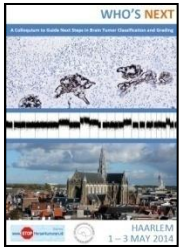
(Additional information : age, location)

Proposals regarding medullobastomas



- The validated major advances in the field need to be incorporated into classification
- Some biological groups (especially subgroups 3 and 4) require more clinical/molecular validation
- Three molecular categories could be introduced: WNT, SHH, non-WNT/non-SHH
- Appropriate molecular tests need to be performed
- Keep the histological part of the classification

Medulloblastoma



Integrated diagnosis:

Histological subtype and molecular subgroup (Wnt, SHH, non-WNT/non-SHH)

Histological diagnosis:

Classic, anaplastic/large cell, desmoplastic/nodular, MBEN

Histological grade:

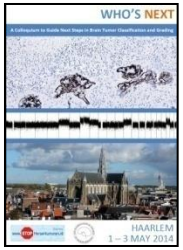
Grade IV [? needed]

Molecular information:

MYC ampl, NMYC ampl, p53+/-, i17q, beta catenin, SMO, PTCH, monosomy 6 (list illustrative and not meant to be exhaustive)

(Additional information, age, location)

Diffuse glioma



Histologic diagnosis

Oligodendroglioma phenotype
Astrocytoma phenotype
Glioblastoma phenotype

Diffuse glioma, indeterminate, "mixed" or ambiguous phenotype

Grade II, III, IV, ungraded
IDH, ATRX, 1p/19q

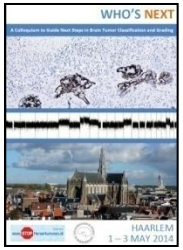
Molecular information

IDH, ATRX, 1p/19q
Grade II, III, IV, ungraded

Integrated Diagnosis

1) Histology and molecular concordant: Diagnosis, grade, molecular findings
2) Indeterminate or mixed histology: Diagnose and grade based on molecular profile
3) Histology and molecular discordant: Diffuse glioma, histologic phenotype, molecular profile
4) Molecular testing not performed: Histologic diagnosis, NOS

Diffuse glioma (1)



Integrated diagnosis:

Histological diagnosis:

Oligodendroglioma phenotype

Histological grade:

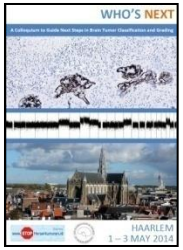
Grade II

Molecular information:

IDHmut, 1p/19q codel

(Frequent)

Diffuse glioma (2)



Integrated diagnosis:

Histological diagnosis:

Anaplastic oligodendroglioma phenotype

Histological grade:

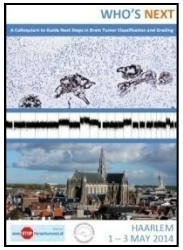
Grade III

Molecular information:

IDHmut, 1p/19q codel

(Frequent)

Diffuse glioma (3)



Integrated diagnosis:

Histological diagnosis:

Diffuse glioma, indeterminate/ambiguous phenotype

Histological grade:

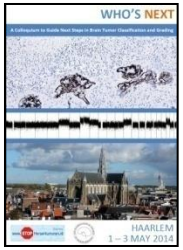
Grade II

Molecular information:

IDHmut, 1p/19q codel

(Frequent)

Diffuse glioma (4)



Integrated diagnosis:

Histological diagnosis:

Diffuse glioma, indeterminate/ambiguous phenotype

Histological grade:

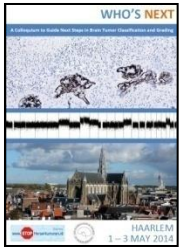
pending [occasional mitoses]

Molecular information:

IDHmut, 1p/19q codel

(Not common)

Diffuse glioma (5)



Integrated diagnosis:

Histological diagnosis:

Astrocytoma phenotype

Histological grade:

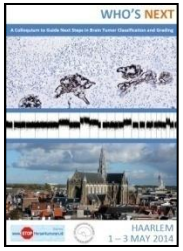
Grade II

Molecular information:

IDHmut, 1p/19q codel, ATRX intact

(Very rare)

Diffuse glioma (6)



Integrated diagnosis:

Histological diagnosis:

Anaplastic oligodendroglioma phenotype

Histological grade:

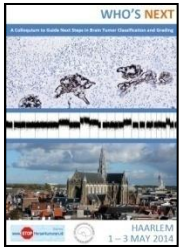
Grade III

Molecular information:

IDHmut, 1p/19q intact, ATRX loss

(Very rare)

Diffuse glioma (7)



Integrated diagnosis:

Histological diagnosis:

Diffuse high-grade glioma with necrosis, indeterminate/ambiguous phenotype [e.g., GBM vs AO]

Histological grade:

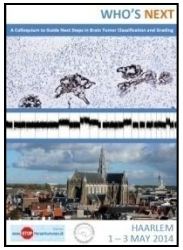
Pending

Molecular information:

IDHwt

(Common)

Diffuse glioma (8)



Integrated diagnosis:

Histological diagnosis:

Diffuse high-grade glioma with necrosis, indeterminate/ambiguous phenotype [e.g., GBM vs AO]

Histological grade:

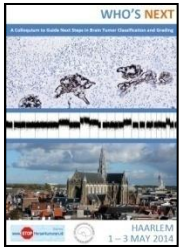
Pending

Molecular information:

IDHmut, 1p/19q codel, ATRX intact

(Occasional)

Diffuse glioma (9)



Integrated diagnosis:

Histological diagnosis:

Diffuse high-grade glioma with necrosis, indeterminate/ambiguous phenotype [e.g., GBM vs AO]

Histological grade:

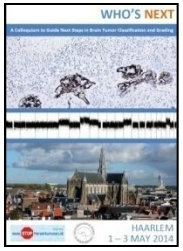
Pending

Molecular information:

IDHmut, 1p/19q intact, ATRX loss

(Uncommon)

Diffuse glioma (10)



Integrated diagnosis:

Histological diagnosis:

Oligodendroglioma phenotype

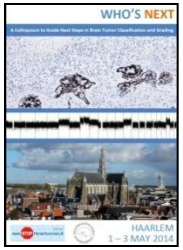
Histological grade:

Grade II

Molecular information:

Not performed

Diffuse Glioma

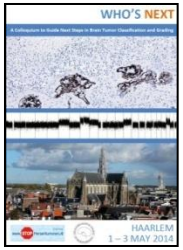


Histologic classification

Molecular information

	Diffuse astrocytoma	Oligodendroglioma	"Oligoastrocytoma" or ambiguous histology
IDH-mut, 1p19q-nondel, ATRX loss			
IDH-mut, 1p19q-del, ATRX intact			
IDH wild type			
Testing not performed			

Diffuse Glioma

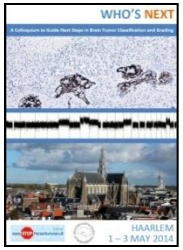


Histologic classification

Molecular information

	Diffuse astrocytoma	Oligodendroglioma	"Oligoastrocytoma" or ambiguous histology
IDH-mut, 1p19q-nondel, ATRX loss	*Diffuse astrocytoma, ATRX loss of expression*		
IDH-mut, 1p19q-del, ATRX intact		*Oligodendroglioma, 1p19q-deleted*	
IDH wild type			
Testing not performed			

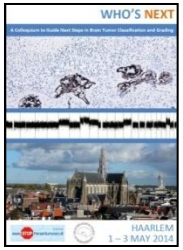
Diffuse Glioma



Histologic classification

Molecular information	Diffuse astrocytoma	Oligodendroglioma	"Oligoastrocytoma" or ambiguous histology
IDH-mut, 1p19q-nondel, ATRX loss			*Diffuse astrocytoma, ATRX loss of expression*
IDH-mut, 1p19q-del, ATRX intact			*Oligodendroglioma, 1p19q-deleted*
IDH wild type			*Diffuse astrocytoma, IDH wild type**
Testing not performed			

Diffuse Glioma

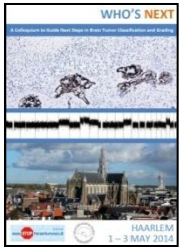


Histologic classification

Molecular information

	Diffuse astrocytoma	Oligodendroglioma	"Oligoastrocytoma" or ambiguous histology
IDH-mut, 1p19q-nondel, ATRX loss	*Diffuse astrocytoma, ATRX loss of expression*		*Diffuse astrocytoma, ATRX loss of expression*
IDH-mut, 1p19q-del, ATRX intact		*Oligodendroglioma, 1p19q-deleted*	*Oligodendroglioma, 1p19q-deleted*
IDH wild type			*Diffuse astrocytoma, IDH wild type**
Testing not performed			

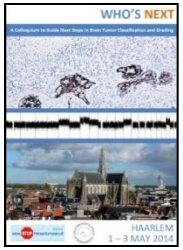
Diffuse Glioma



Histologic classification

Molecular information

	Diffuse astrocytoma	Oligodendroglioma	"Oligoastrocytoma" or ambiguous histology
IDH-mut, 1p19q-nondel, ATRX loss			
IDH-mut, 1p19q-del, ATRX intact			
IDH wild type			
Testing not performed	*Diffuse astrocytoma, NOS*	*Oligodendroglioma, NOS*	*"Diffuse glioma, NOS"*

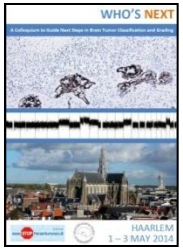


Diffuse Glioma

Histologic classification

Molecular information	**Diffuse astrocytoma**	**Oligodendroglioma**	**"Oligoastrocytoma" or ambiguous histology**
IDH-mut, 1p19q-nondel, ATRX loss	*Diffuse astrocytoma, ATRX loss of expression*		*Diffuse astrocytoma, ATRX loss of expression*
IDH-mut, 1p19q-del, ATRX intact		*Oligodendroglioma, 1p19q-deleted*	*Oligodendroglioma, 1p19q-deleted*
IDH wild type			*Diffuse astrocytoma, IDH wild type**
Testing not performed	*Diffuse astrocytoma, NOS*	*Oligodendroglioma, NOS*	*"Diffuse glioma, NOS"*

Diffuse Glioma

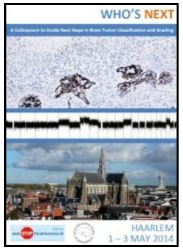


Histologic classification

Molecular information

	Diffuse astrocytoma	Oligodendroglioma	"Oligoastrocytoma" or ambiguous histology
IDH-mut, 1p19q-nondel, ATRX loss			
IDH-mut, 1p19q-del, ATRX intact			
IDH wild type	*Diffuse astrocytoma, IDH wild type**	*Diffuse glioma (oligodendroglioma phenotype), IDH wild type*	*Diffuse astrocytoma, IDH wild type**
Testing not performed			

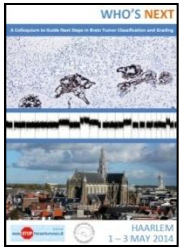
Diffuse Glioma



Histologic classification

Molecular information

	Diffuse astrocytoma	Oligodendroglioma	"Oligoastrocytoma" or ambiguous histology
IDH-mut, 1p19q-nondel, ATRX loss	*Diffuse astrocytoma, ATRX loss of expression*		
IDH-mut, 1p19q-del, ATRX intact		*Oligodendroglioma, 1p19q-deleted*	
IDH wild type			
Testing not performed			



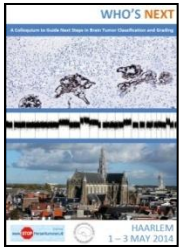
Diffuse Glioma

Histologic classification

Molecular information

	Diffuse astrocytoma	Oligodendroglioma	"Oligoastrocytoma" or ambiguous histology
IDH-mut, 1p19q-nondel, ATRX loss	*Diffuse astrocytoma, ATRX loss of expression*	*Diffuse glioma (oligodendroglioma phenotype), 1p/19q non-deleted, ATRX loss of expression*	
IDH-mut, 1p19q-del, ATRX intact	*Diffuse glioma (astrocytoma phenotype), 1p19q-deleted*	*Oligodendroglioma, 1p19q-deleted*	
IDH wild type			
Testing not performed			

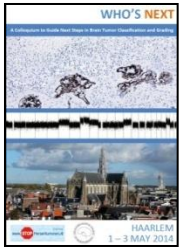
Diffuse Glioma



Histologic classification

Molecular information

	Diffuse astrocytoma	Oligodendroglioma	"Oligoastrocytoma" or ambiguous histology
IDH-mut, 1p19q-nondel, ATRX loss			
IDH-mut, 1p19q-del, ATRX intact			
IDH wild type			
Testing not performed			



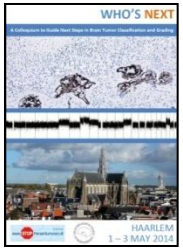
Diffuse Glioma

Histologic classification

Molecular information

	Diffuse astrocytoma	**Oligodendroglioma**	**"Oligoastrocytoma" or ambiguous histology**
IDH-mut, 1p19q-nondel, ATRX loss	*Diffuse astrocytoma, ATRX loss of expression*	*Diffuse glioma (oligodendroglioma phenotype), 1p/19q non-deleted, ATRX loss of expression*	*Diffuse astrocytoma, ATRX loss of expression*
IDH-mut, 1p19q-del, ATRX intact	*Diffuse glioma (astrocytoma phenotype), 1p19q-deleted*	*Oligodendroglioma, 1p19q-deleted*	*Oligodendroglioma, 1p19q-deleted*
IDH wild type	*Diffuse astrocytoma, IDH wild type**	*Diffuse glioma (oligodendroglioma phenotype), IDH wild type*	*Diffuse astrocytoma, IDH wild type**
Testing not performed	*Diffuse astrocytoma, NOS*	*Oligodendroglioma, NOS*	*"Diffuse glioma, NOS"*

Diffuse Glioma

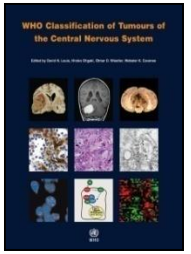


- Grading will follow standard WHO criteria for astrocytoma and oligodendroglioma
- In some, grade may not be possible (diffuse glioma, indeterminate), in which case, either avoid grade or make a comment (e.g., “at least WHO grade”)
- Anaplastic used for WHO grade III astro or oligo
- Glioblastoma used for WHO grade IV astro
- Concern: is it appropriate to grade newly defined molecular subtypes with old morphology criteria?

Outline

- Background on WHO classifications
- Challenges and opportunities for the next WHO classification of nervous system tumors
- The Haarlem meeting and its recommendations
- Next steps for the forthcoming WHO update and a glimpse at future classification systems

WHO classification: working group flow



Do the available clinicopathological and molecular data justify distinct pediatric and adult subtypes?

Is molecular testing *required* or only *suggested* to make the diagnosis, or does the diagnosis remain entirely histological in nature?

If *required*, what is the terminology for histologically compatible tumors that either have discordant molecular profiles or are diagnosed at centers that cannot perform molecular testing?

If *suggested* (but not required) for diagnosis, what is the terminology for otherwise histologically compatible tumors that either have discordant molecular profiles or are diagnosed at centers that cannot perform the molecular tests. Does an "NOS" category need to be created and coded?

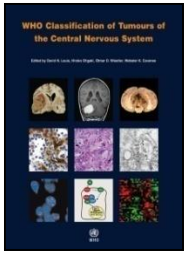
What are the recommended molecular tests?
What are the recommended second-line molecular tests following the initial molecular results?

In the setting of unusual histopathological-molecular combinations, what descriptive diagnoses should be recommended?

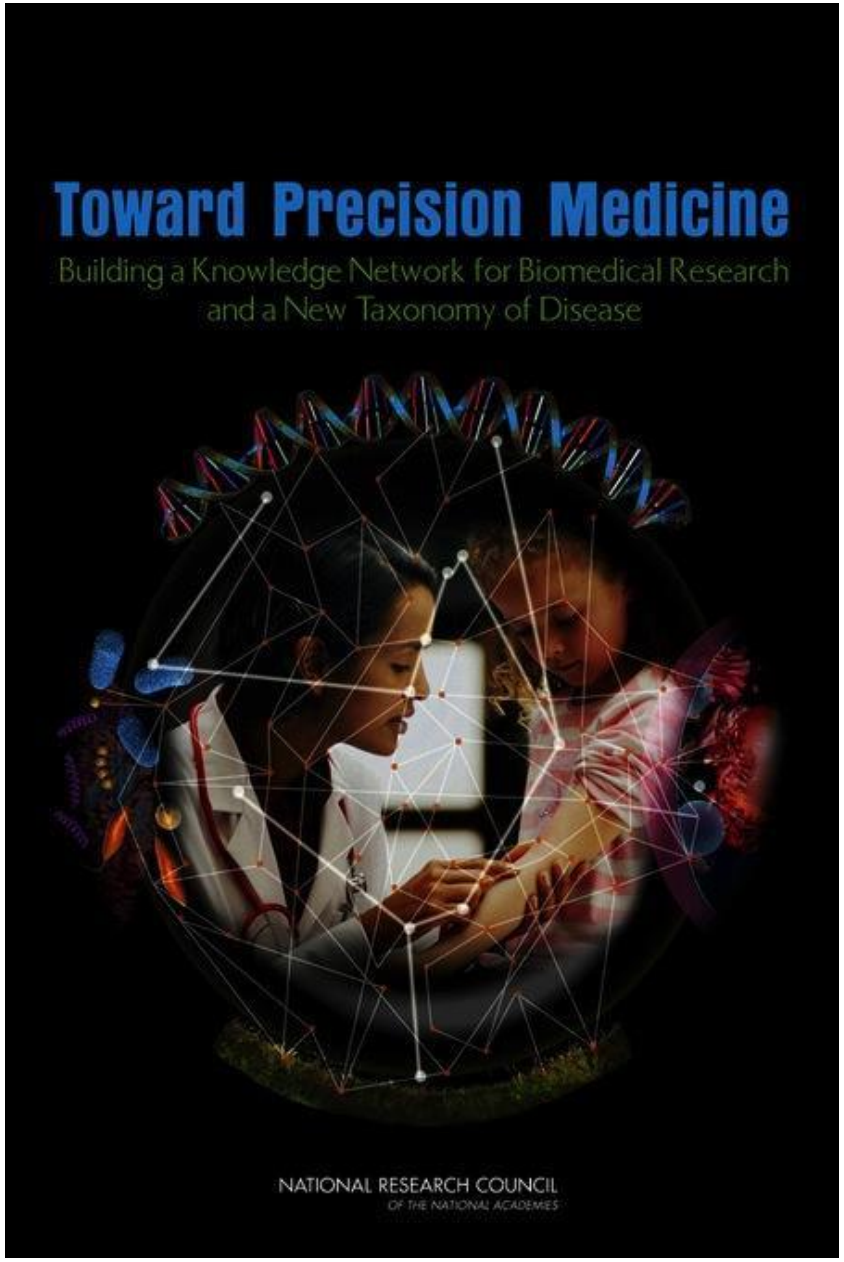
Are there situations in which assigning a WHO grade may be more confusing than helpful? In such situations, should it be recommended that a comment be added to state that the integrated diagnosis may have a different prognosis than suggested in the histological grade?

For each tumor entity with an altered name or definition, should a section entitled "Synonyms" be added to list corresponding prior names of entities?

WHO classification: next steps



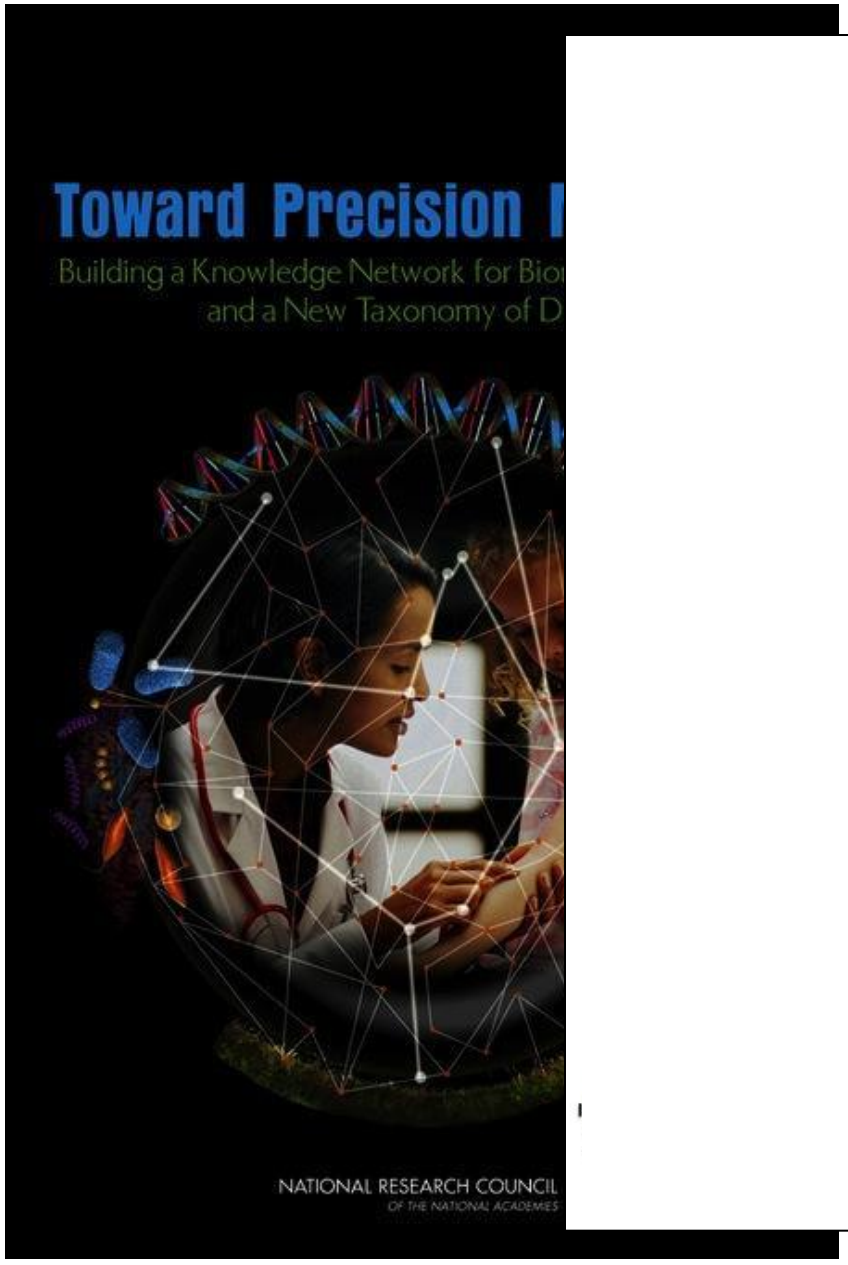
- Establish and publish ISN-Haarlem guidelines that will influence the update of WHO 4th Edition (now-Sept ‘14)
- Process of updating 4th Edition for early 2016:
  - Select group of Senior Reviewers (chosen)
  - Select group of clinical advisors (in discussion)
  - Assign authors to update chapters (Oct ’14)
  - Update chapters via PubCan
  - Plan to solicit input from clinical advisors (before WHO working group meeting)
  - Plan for WHO working group meeting (Heidelberg June ‘15)
  - Probable publication date for 4th Edition update: early ‘16
- 5th Edition → 2018 very earliest



Toward Precision Medicine. Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease

National Academies Press, 2011

"Diagnosis is the foundation of medicine. Accurately and precisely defining a patient's condition does not assure effective treatment, but it is unequivocally the place to start."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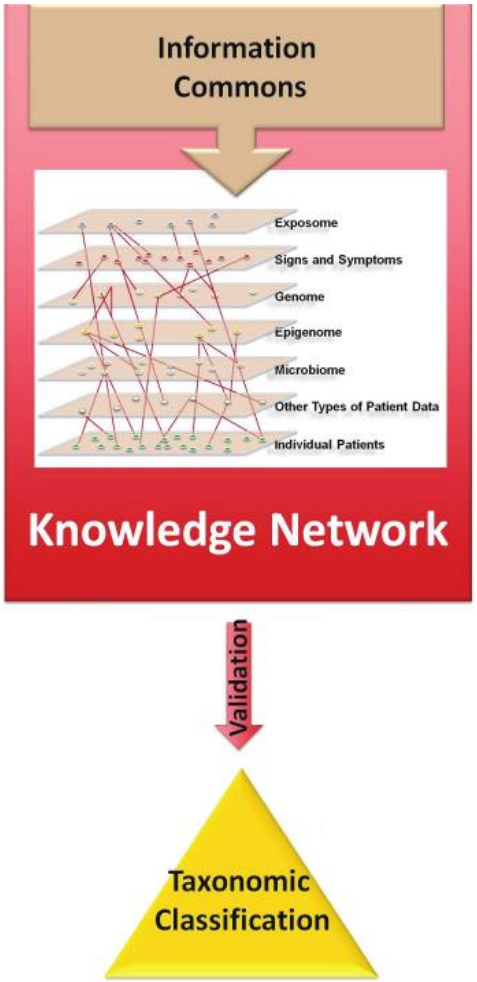
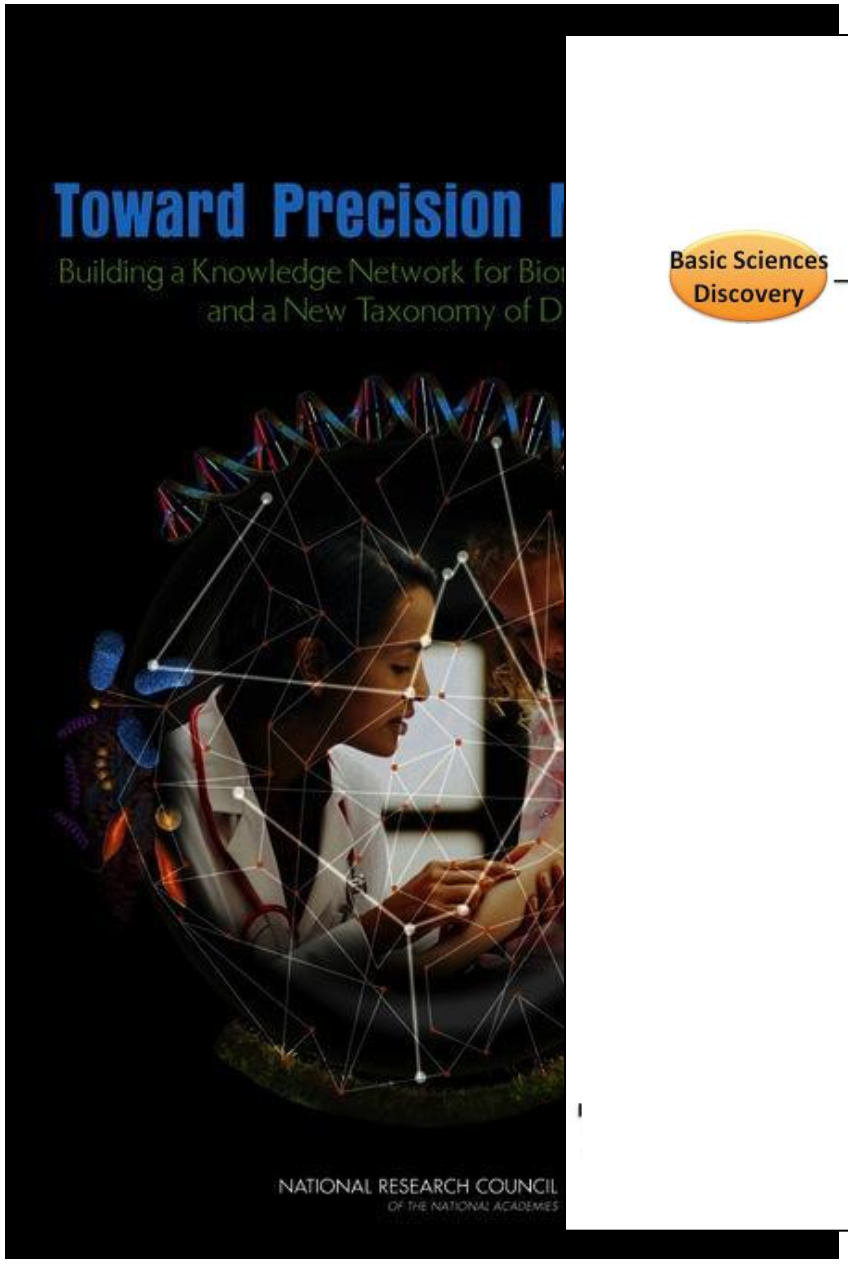

Information Commons
Exposome
Signs and Symptoms
Genome
Epigenome
Microbiome
Other Types of Patient Data
Individual Patients
Knowledge Network
Validation
Taxonomic Classification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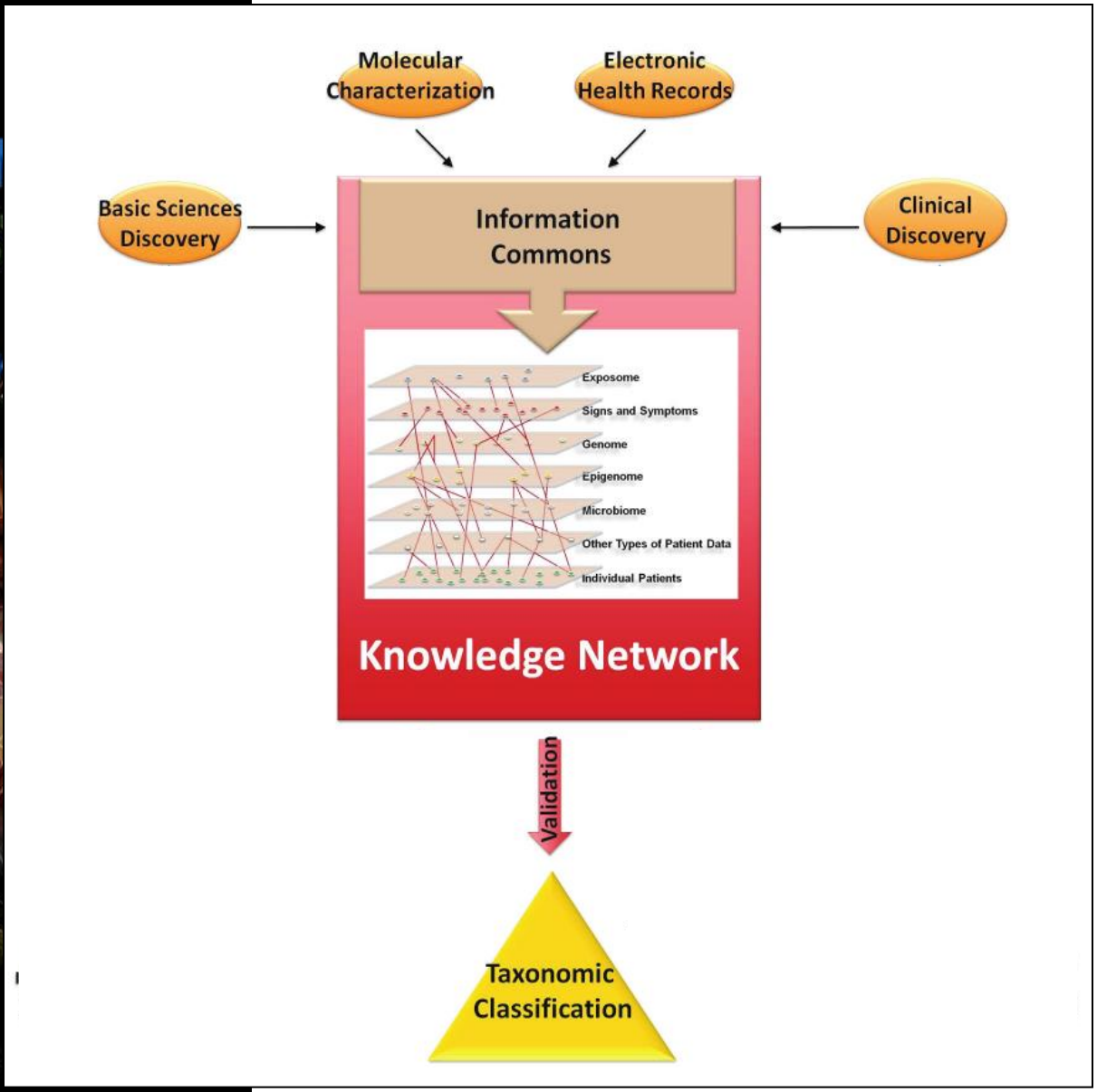
Molecular Characterization
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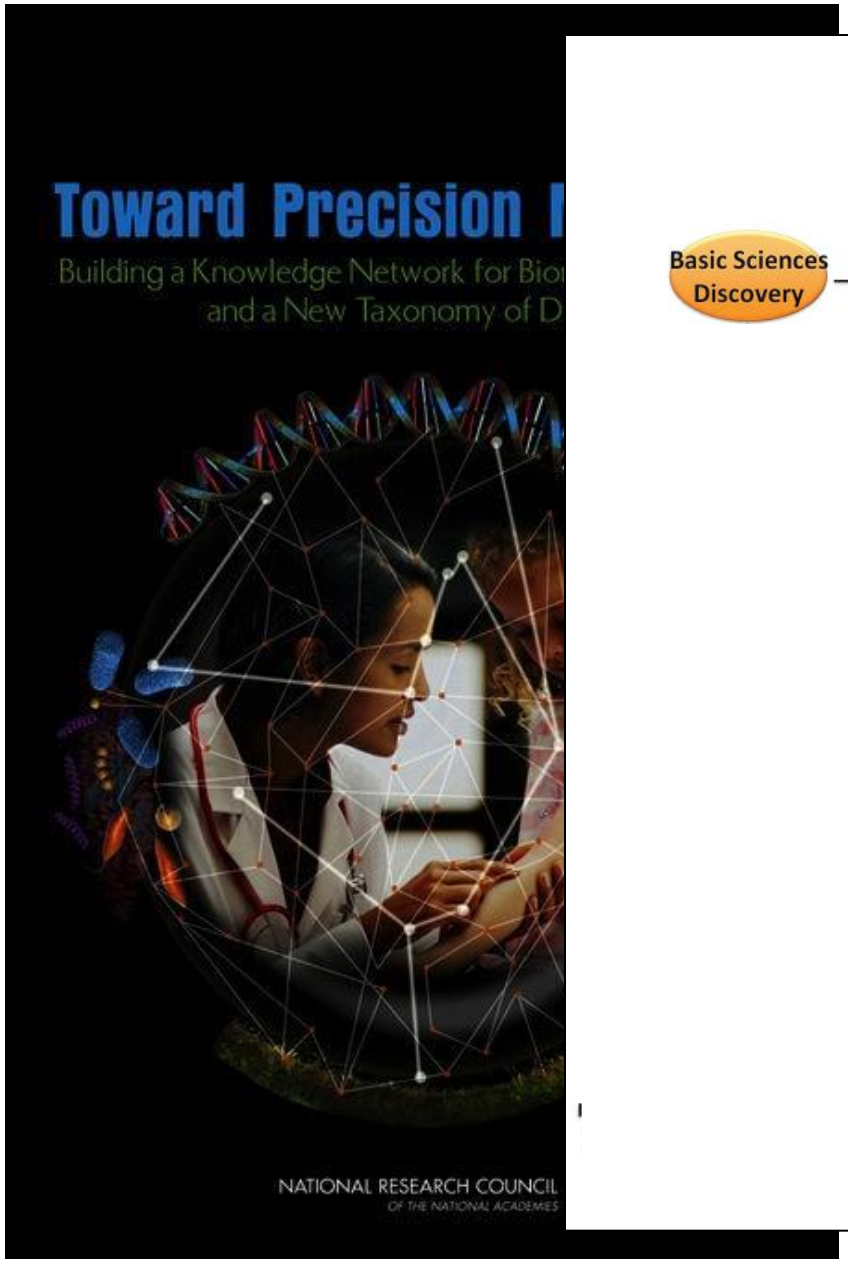
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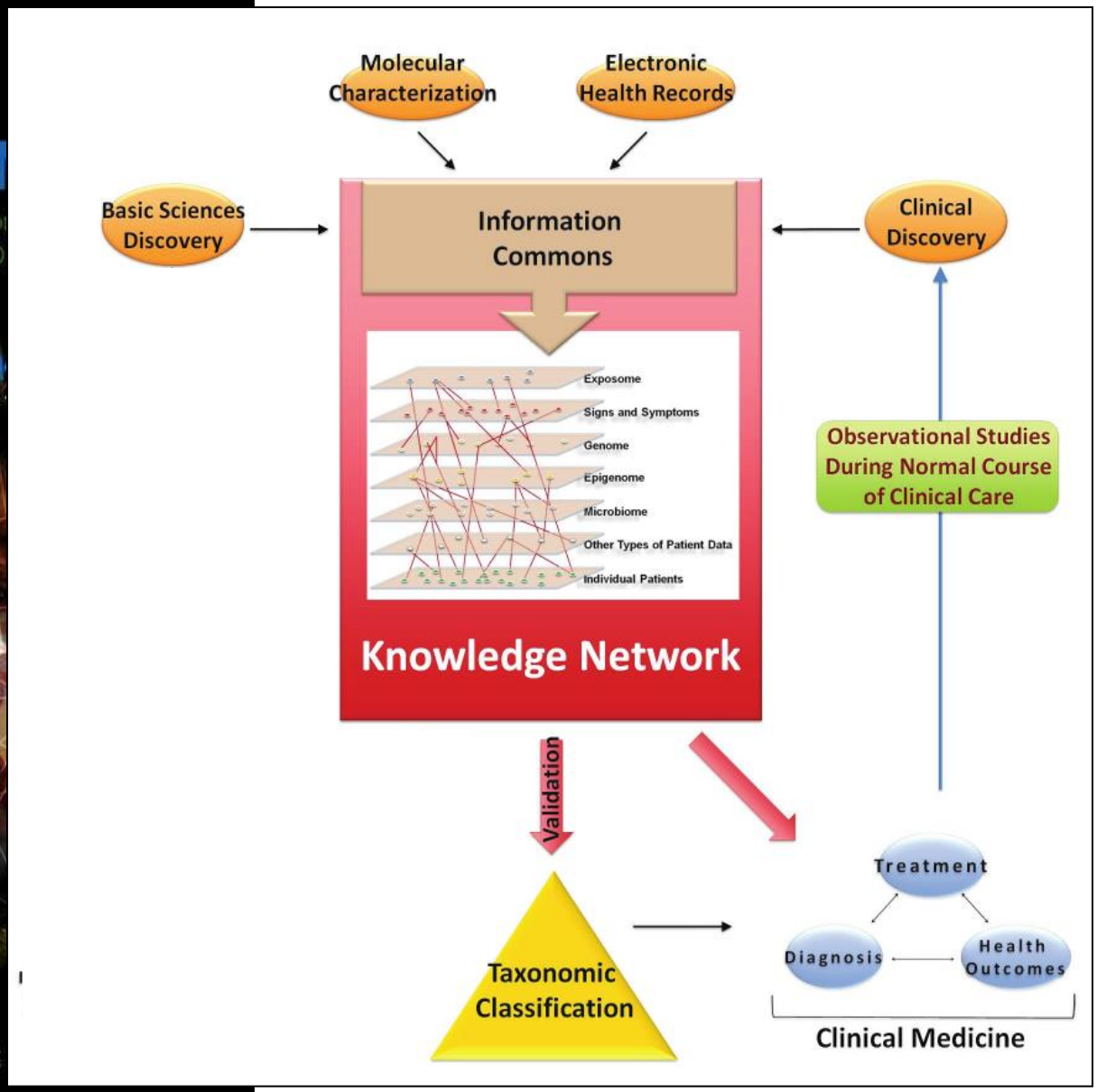
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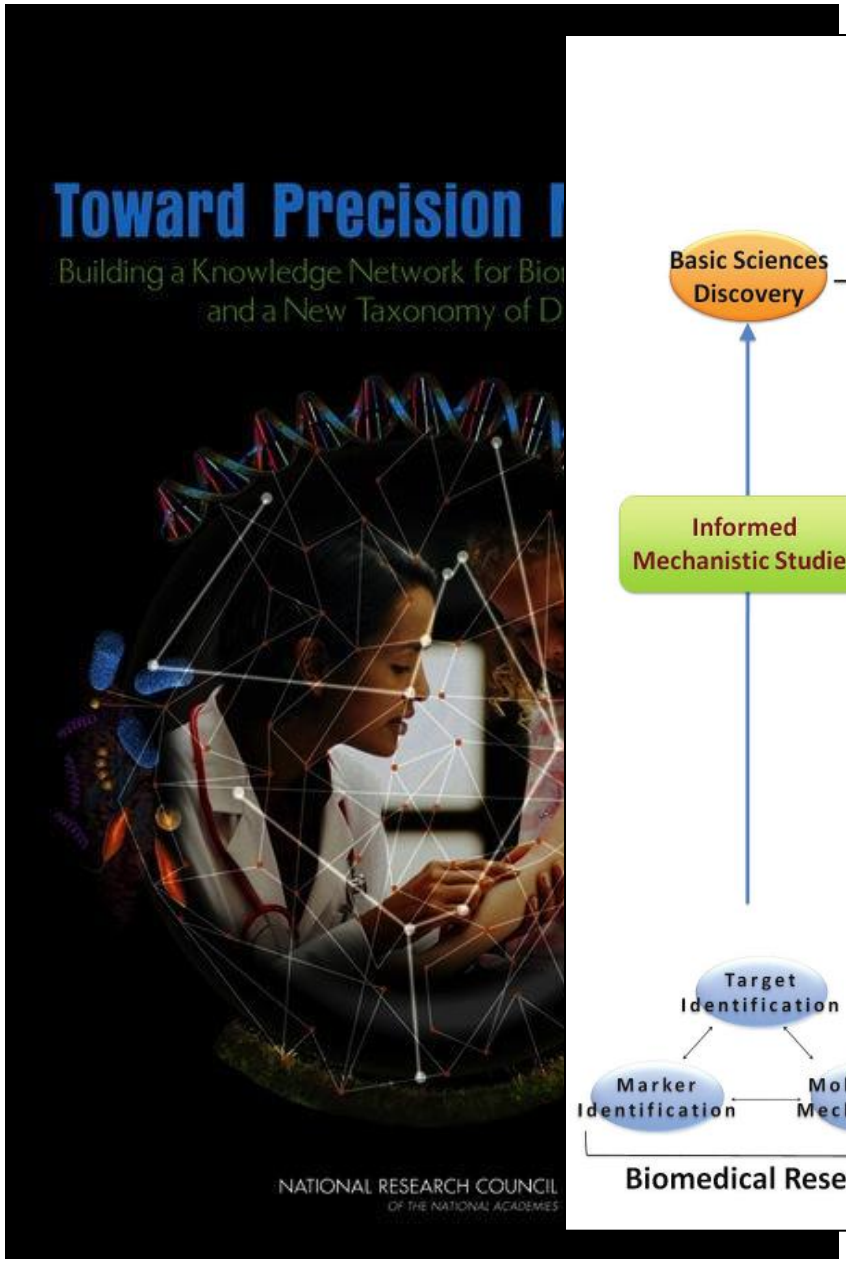
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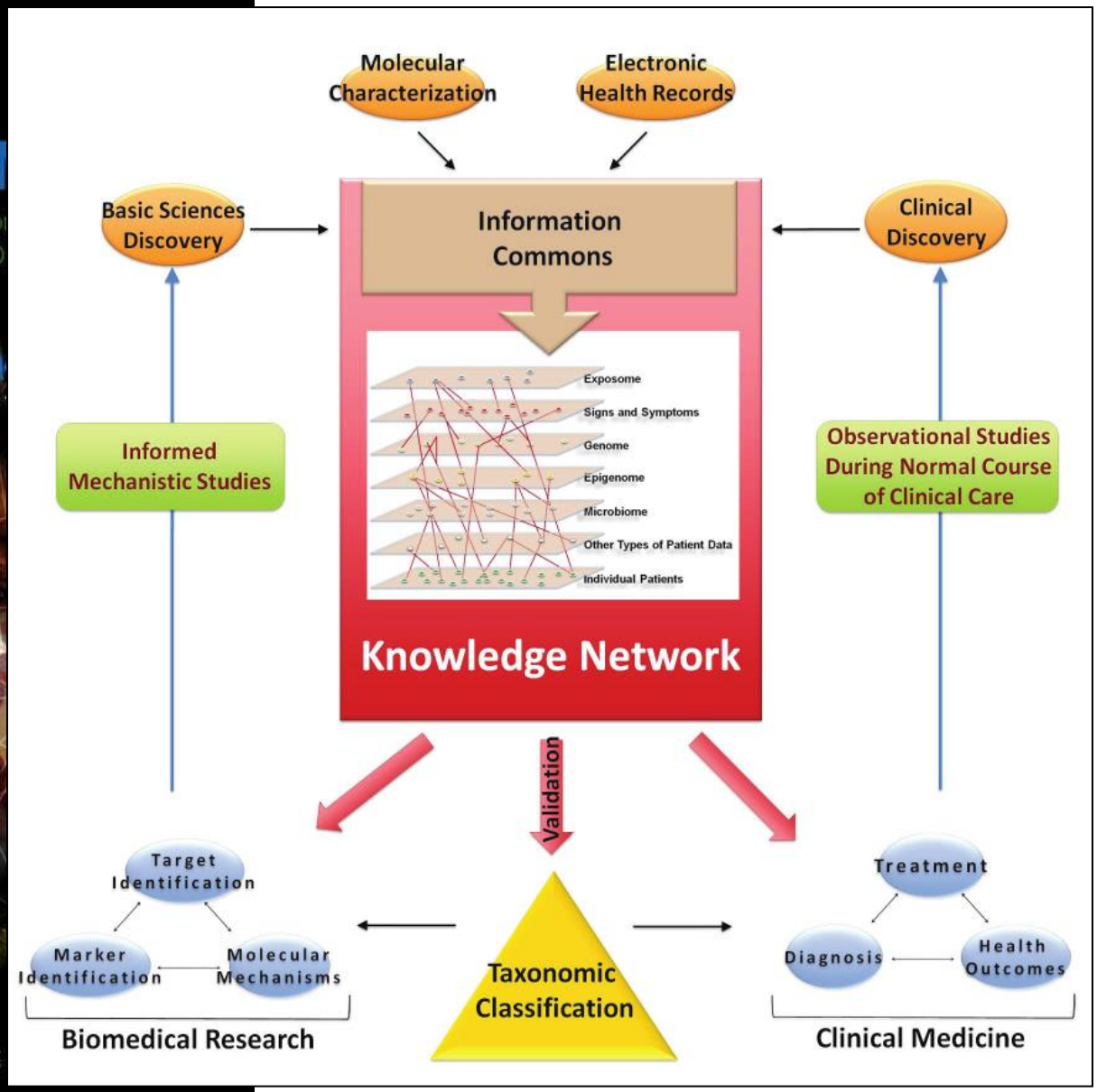
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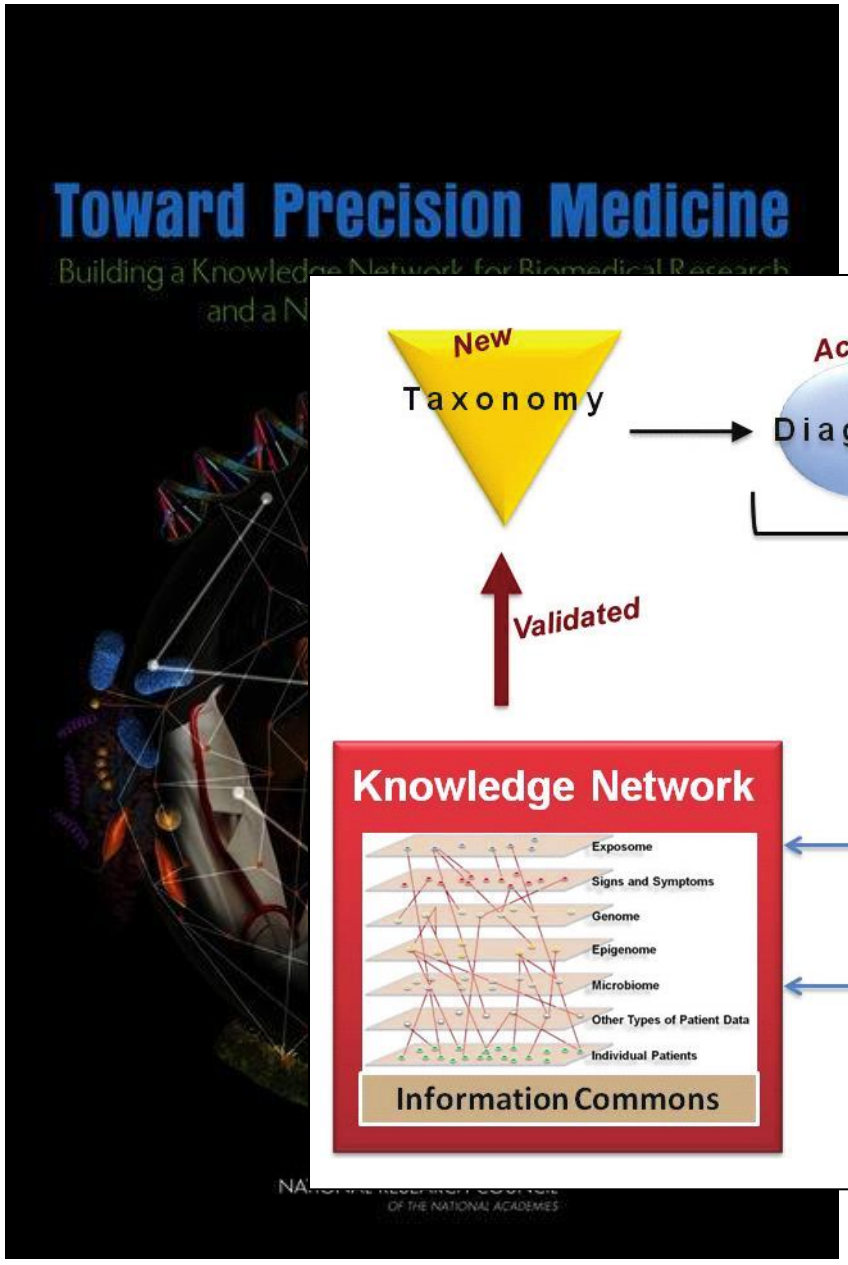
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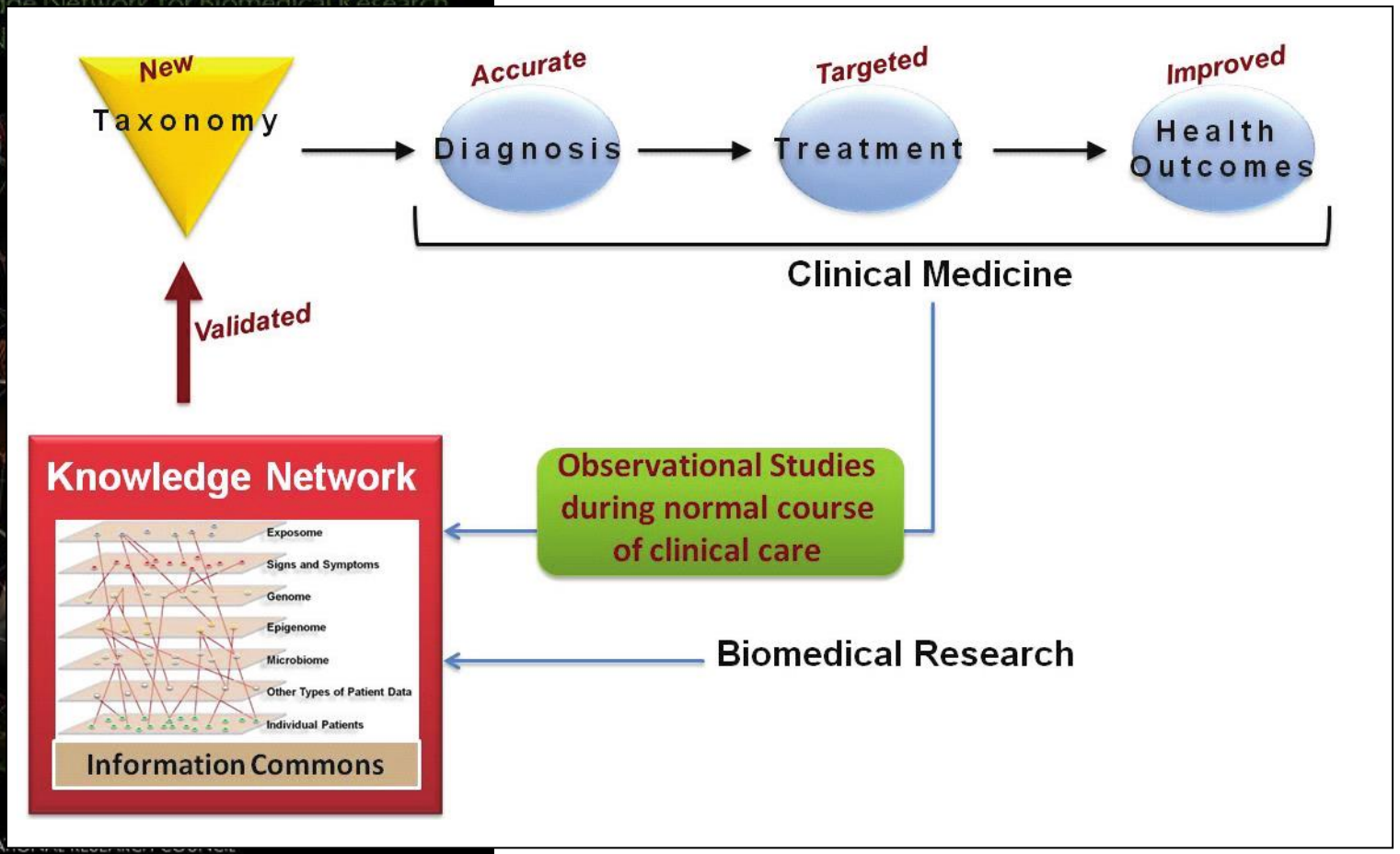
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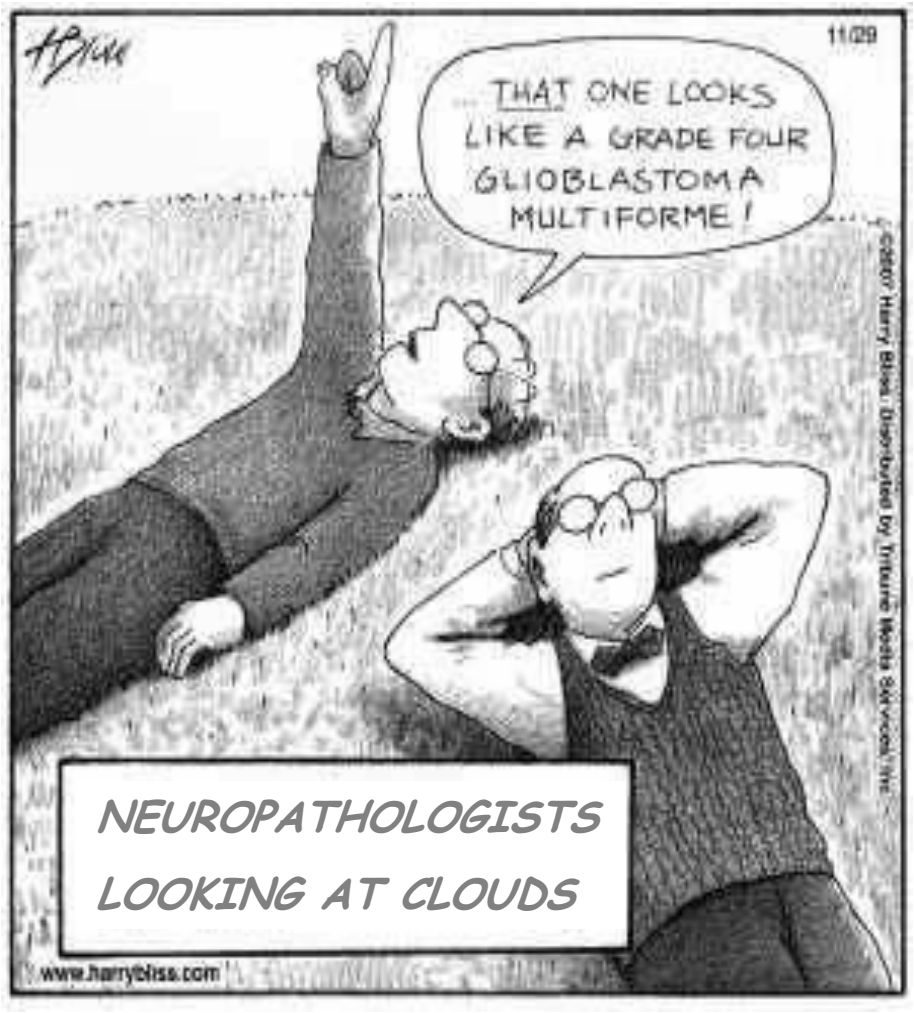
Advancing Diagnosis and Discovery



WHO's next?

Suggested guidelines for the next WHO classification of brain tumors

David N. Louis, M.D.

Pathologist-in-Chief, MGH
Benjamin Castleman Professor of Pathology, HMS

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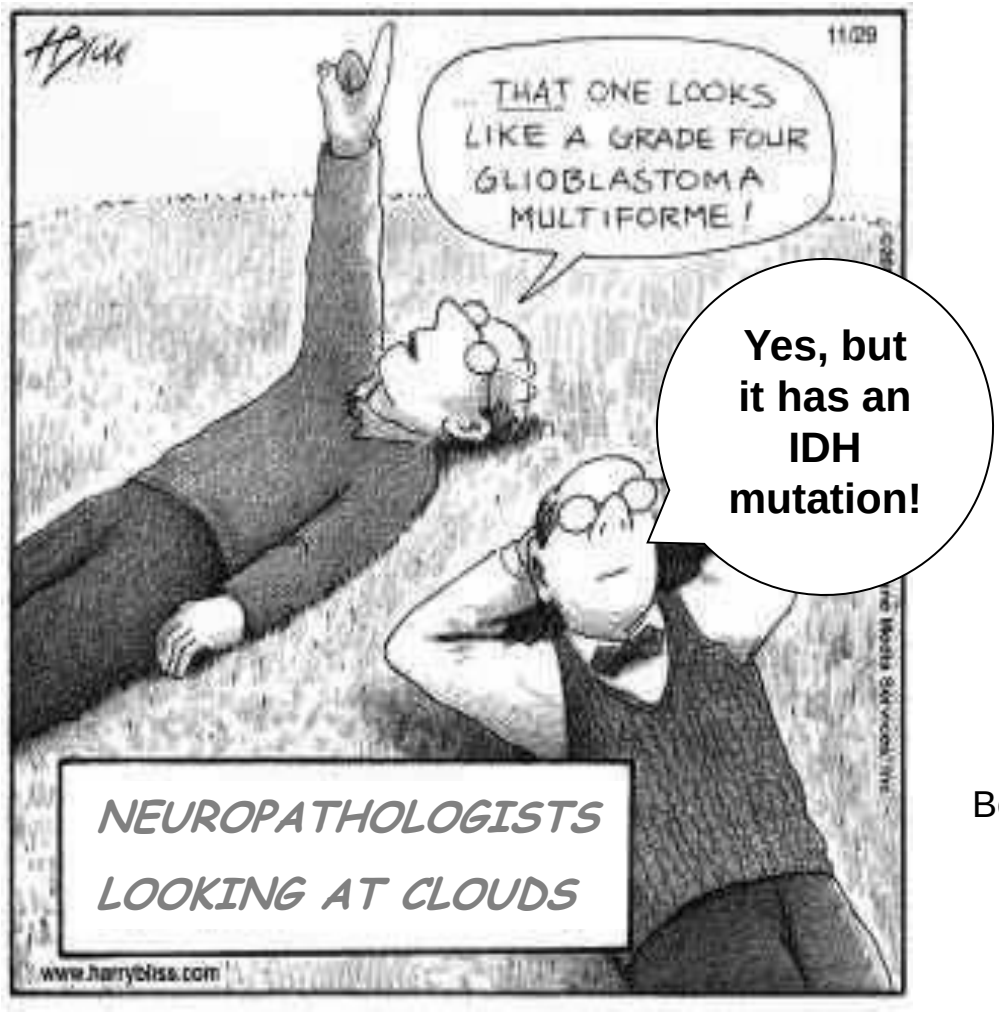

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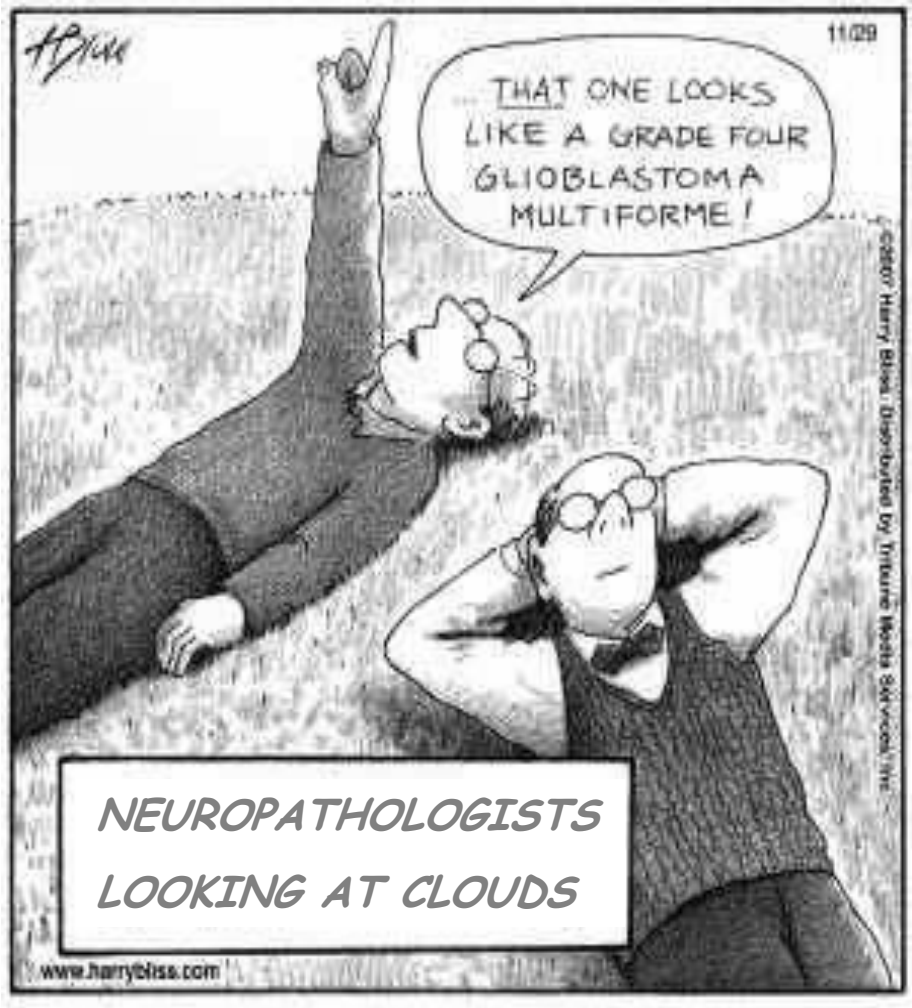

"WHO's next?" The past, present and future of brain tumor classification

David N. Louis, M.D.

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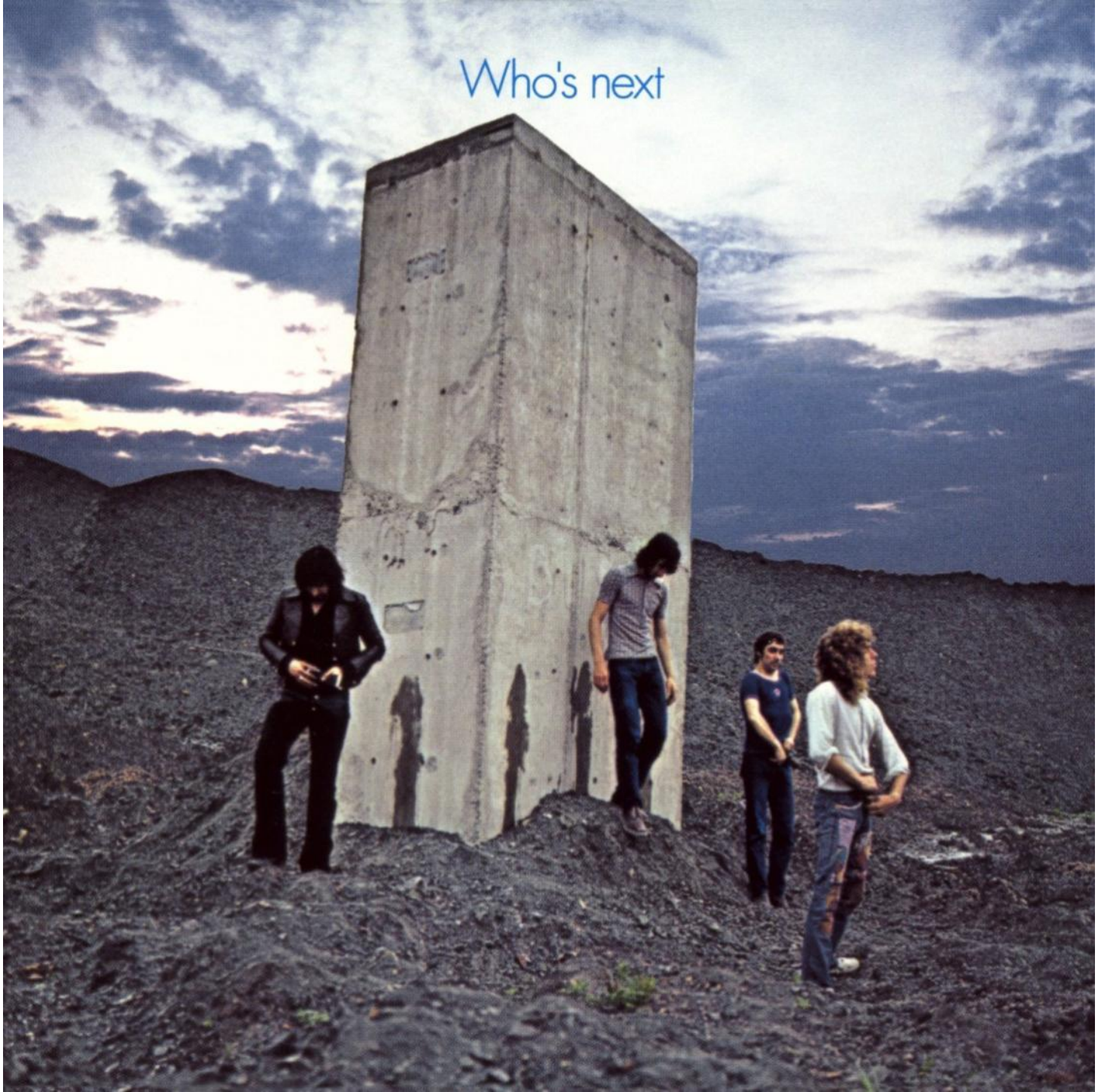
- The focus will be on the two areas in which the greatest progress has been made in unravelling molecular aberrations associated with the oncogenesis of brain tumors:
  - Gliomas (including adult and pediatric glioblastoma, oligodendroglioma, pilocytic astrocytoma and pleomorphic xanthoastrocytoma)
  - Embryonal tumors (including medulloblastoma and atypical teratoid/rhabdoid tumor (AT/RT)).
- Discussions of these two groups should provide a conceptual framework for other brain tumor types as well.

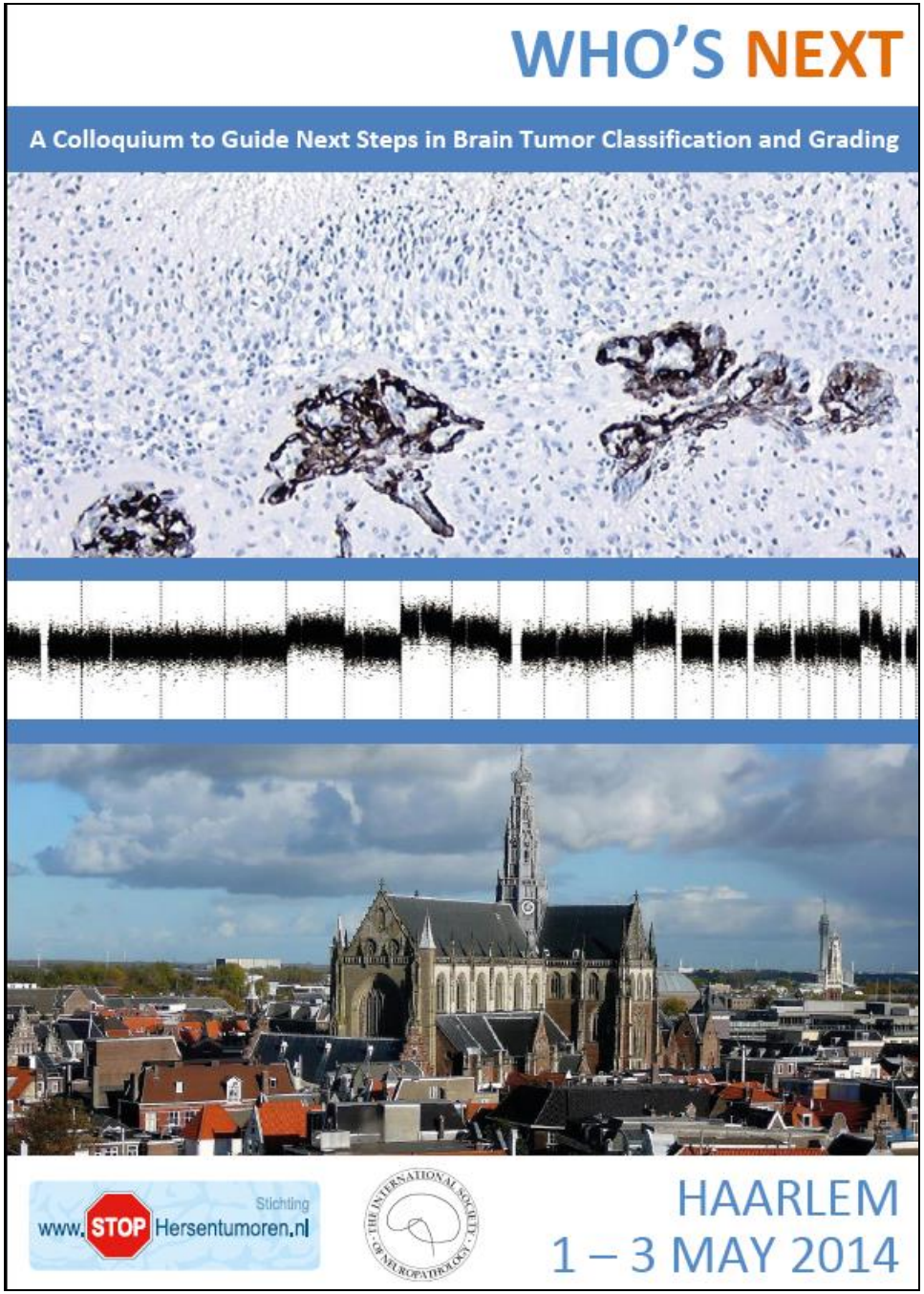
Goal, method and output

- Our goal is to answer the question of whether non-histological criteria (e.g., molecular, imaging, clinical, other?) be used to enhance typing and grading of human brain tumors?
- Our method will be based on open, consensus-seeking discussions informed by peer-reviewed data as well as our experiences and those of our colleagues
- Our output will be published guidelines that aim to inform the next WHO classification

Caveats

- This is NOT an official WHO meeting
- This is NOT an official WHO meeting
- Therefore, our goal is NOT to define specific entities
- It is important to express your informed opinions and to relay those of your neuro-oncology colleagues
- Opinions based on (published) data are preferable...
- ... but it is recognized that guidelines for future use involve a certain amount of “informed suggestions”...
- ... With (importantly) such informed suggestions being based on open, consensus-seeking discussions


Who's next



"WHO's Next?"

A Colloquium to Guide Next Steps in Brain Tumor Classification and Grading

Sponsored by the International Society of Neuropathology

Made possible through generous support from the STOPbraintumors Foundation

Organizers:

- ***David Louis***
- ***Pieter Wesseling***
- ***Arie Perry***

Program Committee:

- ***Peter Burger***
- ***David Ellison***
- ***Guido Reifenberger***
- ***Andreas von Deimling***