Genomic Analysis of Human Tumors with SNP Microarrays

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The Methodist Hospital, Houston TX

Outline

• Introduction
  • Copy Number Changes & LOH
  • SNP Arrays
• Clinical Utility
  • Renal Cell Carcinoma
  • Hematologic Malignancies
  • Brain Tumors
  • Others
• Conclusions

Disclaimer: Co-founder of iKaryos Diagnostics, a company that intends to offer diagnostic assays based on this technology.

DNA Copy Number Changes in Tumor Cells

Normal cell

Homologous repeats
Segmental duplications
Chromosomal rearrangements
Duplicative transpositions
Non-allelic recombinations

Tumor cells

deletion
gains

CN=0  CN=1  CN=2  CN=3  CN=4
Loss-of-Heterozygosity

- At any locus, you have 2 alleles: one paternal and one maternal
- Each allele is either A or B
  - AA (homozygous A)
  - BB (homozygous B)
  - AB (heterozygous)

Copy Neutral LOH

![Copy Neutral LOH Diagram]

A B A B A B
Genotype: Het Het LOH
Copy Num: CN = 2 CN = 2 CN = 1

Copy Neutral LOH

Acquired Uniparental Disomy (UPD)

From: http://en.wikipedia.org/wiki/Virtual_Karyotype

How Do We Detect Copy Number Changes?

Traditional Methods

- **Karyotyping**
  - Can see the whole genome
  - Course resolution
  - Difficult to interpret; need highly skilled technicians (hard to find)
  - Must culture cells (need fresh tissue)
  - Cannot use FFPE

- **FISH (fluorescent in situ hybridization)**
  - Cannot see the whole genome
  - Low resolution: 1 probe per chromosomal arm
  - Probes are expensive
  - Need highly skilled technicians
  - Does not perform well on FFPE for monosomy/trisomy

- **LOH analysis with microsatellites (LOH = loss)**
  - Cannot see the whole genome
  - Need normal tissue to compare
  - Low resolution: 2-3 markers per region evaluated
  - Can use FFPE tissues
How Do We Detect Copy Number Changes?

New Methods

- **Multiplex Ligation-Dependent Probe Amplification (MLPA)**
  - Simple method to quantify up to 45 nucleic acid sequences in a single reaction.
  - Targeted Only
  - Fresh or FFPE tissues
  - Need reference sample
  - Cannot do LOH

- **Array Comparative Genomic Hybridization (aCGH)**
  - Whole genome or targeted
  - High resolution (1Mb – 35Kb)
  - Fresh or FFPE tissues
  - Need reference sample
  - Cannot do LOH

- **SNP Genotyping Arrays**
  - Whole genome
  - High resolution (200 – <6 Kb) 400 8K probes/ arm
  - Fresh or FFPE tissues
  - Does NOT need reference sample
  - Can do LOH

What is a SNP Array?

- 25-mer oligonucleotide probes complimentary to the SNP of interest.
- Obtain hybridization intensity values for each probe set
  - Genotype (AA, AB, or BB)
  - Copy number
- Reconstruct genome in silico → Virtual ‘karyotype’
  - Line the SNPs up in chromosomal order
  - Look for consecutive SNPs with same change

Importance of Allele-Specific Analysis

10K 2.0 arrays, FFPE, pediatric glial tumors
SNP Arrays

What they can do
- Genome wide
- High resolution
- Aneuploidies/copy number/amplifications
- Genotype/LOH
- Copy neutral LOH/UPD
- Whole genome association studies
- Whole genome methylation status

What they can't do
- Balanced translocations
- Inversions
- Over-expression by mechanisms other than gene amplification

Applications
- Constitutional Genetics
- Cancer
  - Diagnostics
  - Prognostics
  - Therapeutics
  - Drug eligibility

Special Considerations for Cancer

- Hematopathologists always get fresh tumor samples
  - Flow cytometry is routine and can guide tumor enrichment strategies
  - Sample types: bone marrow aspirate, peripheral blood, lymph node, spleen

- Surgical pathologists very rarely get fresh tumor samples
  - They do not know they want/need an ancillary study until they look at it under the microscope.
  - They are refractory to pleas from molecular pathologists to change this behavior.
  - Assay must work on FFPE.
  - Manual microdissection can be done for tumor enrichment with visual estimation of normal clone contamination.

Optimization of the Affymetrix GeneChip Mapping 10K 2.0 Assay for Routine Clinical Use on Formalin-fixed Paraffin-embedded Tissues

<table>
<thead>
<tr>
<th>Parameter</th>
<th>10K 2.0</th>
<th>500K</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Registration (min)</td>
<td>25</td>
<td>45</td>
<td>20</td>
</tr>
<tr>
<td>Loading (min)</td>
<td>30</td>
<td>45</td>
<td>15</td>
</tr>
<tr>
<td>Optimization (min)</td>
<td>15</td>
<td>25</td>
<td>10</td>
</tr>
<tr>
<td>Washing &amp; Staining (min)</td>
<td>30</td>
<td>45</td>
<td>15</td>
</tr>
</tbody>
</table>

Table 1: Agreement in 100 Cases
Experience on FFPE

<table>
<thead>
<tr>
<th>Platform</th>
<th># of Samples</th>
<th>Interpretable</th>
<th>Success Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>10K Xba 2.0</td>
<td>255</td>
<td>192</td>
<td>76.3%</td>
</tr>
<tr>
<td>250K Nsp</td>
<td>206</td>
<td>158</td>
<td>76.7%</td>
</tr>
<tr>
<td>Both</td>
<td>442</td>
<td>336</td>
<td>76%</td>
</tr>
</tbody>
</table>

*Difference in total number due to samples excluded from hybridization and samples that were processed in both platforms. Note: Samples run in 3 different laboratories (UPMC, TMH & Creighton).

Virtual Karyotyping on FFPE Samples

- Virtual karyotyping with SNP arrays can be successful in 80-90% of samples with excellent reproducibility.
- Important factors to consider:
  - Adequate storage of FFPE blocks (temperature/humidity)
  - Careful selection of areas with minimal necrosis and stromal contamination
  - QC parameters to avoid low quality samples.
- As expected, genetic tumor heterogeneity is present when analyzing different tumor regions.
  - More frequent heterogeneity seen when analyzing different tissue blocks.
- SNP arrays are a reliable platform for the analysis of chromosomal copy number and LOH alterations in FFPE tissues which can be used in the clinical environment.

Renal Epithelial Tumors

- [Image of renal epithelial tumors]
Diagnostic Utility of SNP Arrays

Morphologically Challenging Tumors

- Spindle cells
- Mixed types
- Oncocytic tumors

Molecular Dx of Renal Tumors

- This knowledge has not been incorporated into routine clinical practice.
  - Cytogenetics – needs fresh tissue
  - Microsatellite LOH – multiple PCRs required
  - Fluorescence in-situ hybridization (FISH) – multiple probes

Frequency of classic chromosomal aberrations in renal epithelial neoplasms.

<table>
<thead>
<tr>
<th>Type of Renal Tumor</th>
<th>Chromosomal Aberrations</th>
<th>% Cases with Chromosomal Abnormality</th>
<th>Platform</th>
<th>Comment</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clear Cell RCC</td>
<td>del(3)(p): 3p14, 3p21, 3p25-26</td>
<td>81%</td>
<td>aCGH</td>
<td>Yoshimoto et al. 2007</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>98%</td>
<td>CG</td>
<td>Gunawan et al. 2001</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>98%</td>
<td>LOH</td>
<td>Bugert &amp; Kovacs 1996</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>100%</td>
<td>FISH</td>
<td>Receveur et al 2005</td>
<td></td>
</tr>
<tr>
<td>Papillary RCC</td>
<td>Trisomy 7 and 17</td>
<td>67%/43%</td>
<td>FISH</td>
<td>Lager et al. 1995</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>100%</td>
<td>CG</td>
<td>Jiang et al 1998</td>
<td></td>
</tr>
<tr>
<td>Chromophobe RCC</td>
<td>Loss of: 1, 2, 6, 10, 13, 17 and/or 21</td>
<td>100%</td>
<td>aCGH</td>
<td>Yoshimoto et al. 2007</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>95%</td>
<td>LOH</td>
<td>Bugert &amp; Kovacs 1996</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>74%</td>
<td>FISH</td>
<td>Brunelli et al. 2005</td>
<td></td>
</tr>
<tr>
<td>Oncocytoma</td>
<td>Chr 1 loss or normal</td>
<td>100%</td>
<td>FISH</td>
<td>Brunelli et al. 2005</td>
<td></td>
</tr>
</tbody>
</table>

Individual Profiles of Renal Tumors

- Clear Cell
- Papillary
- Chromophobe

-3p
+7
+17
-1
-2
-6
-10
-13
-17
-1p36, -1q32-pter

Clear Cell

Papillary

Chromophobe
Summary Profiles of Renal Tumors

Diagnostic Applications in Renal Tumors

• Taking into account both studies, we have shown that virtual karyotyping can classify 92% of challenging renal tumors (37 of 40).
• 2 cases with novel pattern: CRCC vs. ChRCC
• 1 case with novel pattern: possible PRCC type 2

Prognostic Markers

Proposed prognostic chromosomal aberrations in ccRCC.

<table>
<thead>
<tr>
<th>Prognostic Chromosomal Aberration</th>
<th>% Cases with Chromosomal Abnormality</th>
<th>Platform</th>
<th>Ref</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>38% 26 aCGH (12) Low vs. high grade (P = 0.0143)</td>
<td>38%</td>
<td>aCGH</td>
<td>(12)</td>
<td>Low vs. high grade (P = 0.0143)</td>
</tr>
<tr>
<td>31% 52 LOH (13) Low vs. high stage</td>
<td>31%</td>
<td>LOH</td>
<td>(13)</td>
<td>Low vs. high stage</td>
</tr>
<tr>
<td>48% 88 LOH (14) Low vs. high stage / nuclear grade</td>
<td>48%</td>
<td>LOH</td>
<td>(14)</td>
<td>Low vs. high stage / nuclear grade</td>
</tr>
<tr>
<td>39% 130 LOH (15) Higher disease specific mortality in low stage tumors</td>
<td>39%</td>
<td>LOH</td>
<td>(15)</td>
<td>Higher disease specific mortality in low stage tumors</td>
</tr>
<tr>
<td>21% 118 CG (16) Metastasis at Diagnosis (P = 0.006)</td>
<td>21%</td>
<td>CG</td>
<td>(16)</td>
<td>Metastasis at Diagnosis (P = 0.006)</td>
</tr>
<tr>
<td>18% 73 FISH (17) 5y-CSS 43% vs. 88% (P &lt; 0.001)</td>
<td>18%</td>
<td>FISH</td>
<td>(17)</td>
<td>5y-CSS 43% vs. 88% (P &lt; 0.001)</td>
</tr>
<tr>
<td>Poor 9p-</td>
<td>9p-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good 5q+</td>
<td>56.8%</td>
<td>CG</td>
<td>(16)</td>
<td>Better OS (P = 0.001)</td>
</tr>
</tbody>
</table>


Chromosomal Loss by Stage

Chromosomal Loss by Nuclear Grade

Frequency of chromosome 14q and 9p losses in clear cell carcinoma by pathologic tumor stage (A) and by nuclear grade (B). FG = Fuhrman Nuclear Grade.
Chromosomal imbalances are useful for recurrence prognosis in RCC.

Hematologic Malignancies

CLL: Prognostic Indicators

Five main genetic aberrations are recognized in CLL that have a major impact on disease behavior.


Several clinical validation studies have shown SNP arrays have >95% concordance with the standard CLL FISH panel. In addition, many studies using array-based karyotyping have identified ‘atypical deletions’ missed by the standard FISH probes and acquired uniparental disomy at key loci for prognostic risk in CLL.

CLL with no abnormalities by FISH panel.

Capturing Genomic Complexity in One Assay
This CLL sample did not show any copy number abnormalities using the standard CLL FISH panel, while the SNP array karyotype captures the genomic complexity of this case, including acquired uniparental disomy (UPD) of 1q and 10q.

![Image of FISH test results]

Slide courtesy of Jill Hagenkord, MD, Creighton Medical Labs

Prognosis in Multiple Myeloma

- del(12p13.31) is an independent adverse marker
- amp(5q31.1) is a favorable marker
- Lack of a proliferative clone makes conventional cytogenetics informative in only ~30% of cases.

![Image of cytogenetic analysis results]

Myelodysplastic Syndrome

- Cytogenetics play a decisive role in the WHO classification.
- Good Prognosis:
  - normal karyotype, isolated del(5q), isolated del(20q), Y
- Poor Prognosis:
  - complex abnormalities (ie, >3 abnormalities), -Y del(17q)
- Intermediate Prognosis:
  - all other abnormalities.
- aUPD seen frequently in patients with MDS, believed to be a pathogenic mechanism.
- aUPD of chromosome 7 associated with poor prognosis in patients with normal karyotypes.

![Image of cytogenetic analysis results]


**Note:** Images and data are for educational purposes and should not be used for clinical decision-making. Always consult with a qualified healthcare professional for accurate diagnosis and treatment.
Clinically relevant UPD detected by SNP array karyotyping

Table 1: Subtelomeric variations consistent with segmental UPD.

<table>
<thead>
<tr>
<th>Type</th>
<th>Gene</th>
<th>Disease</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>UPD2q</td>
<td>ARF</td>
<td>MDS</td>
<td>Kornblau et al. (2000), 2001</td>
</tr>
<tr>
<td>UPD2q</td>
<td>ATER/ER</td>
<td>MDS</td>
<td>Pugh et al. (2003)</td>
</tr>
<tr>
<td>UPD2q</td>
<td>NFI</td>
<td>SM</td>
<td>Flocks et al. (2004)</td>
</tr>
<tr>
<td>UPD2q</td>
<td>RNF</td>
<td>sHLL</td>
<td>Kant ch et al. (2004)</td>
</tr>
<tr>
<td>UPD11q</td>
<td>RPS6</td>
<td>MDS</td>
<td>Caligiuri et al. (2003)</td>
</tr>
<tr>
<td>UPD11q</td>
<td>NR1D1</td>
<td>AML</td>
<td>Pugh et al. (2003)</td>
</tr>
<tr>
<td>UPD11q</td>
<td>UHRF1</td>
<td>MDS</td>
<td>Pugh et al. (2003)</td>
</tr>
<tr>
<td>UPD10q</td>
<td>RPS10</td>
<td>AML</td>
<td>Pugh et al. (2003)</td>
</tr>
<tr>
<td>UPD10q</td>
<td>NF1</td>
<td>Unpublished observations</td>
<td></td>
</tr>
<tr>
<td>UPD10q</td>
<td>NF2</td>
<td>NF2</td>
<td>Caligiuri et al. (2004)</td>
</tr>
<tr>
<td>UPD10q</td>
<td>AR</td>
<td>MDS</td>
<td>Pugh et al. (2003)</td>
</tr>
<tr>
<td>UPD10q</td>
<td>DDX6</td>
<td>Unpublished observations</td>
<td></td>
</tr>
</tbody>
</table>

Hematologic malignancies only.
Similar review of solid tumor literature has not been published.


Slide courtesy of Jill Hagenkord, MD, Creighton Medical Labs

Neuropathology

Molecular Classification of Glial Tumors

- **Oligodendroglia** $$1p/19q$$ Co-deletion (60%)
  - Diagnostic
    - Differentiates oligodendrogliomas (OG) from astrocytomas (AS)
    - Must be deletion of entire 1p arm (not partial, G AS)
    - Do not have p53, PTEN, EGFR amp, etc assoc with AS
  - Prognostic
    - Prolonged natural history
  - Predictive
    - Powerful predictor of response to chemotherapy
    - MGMT overexpression $$\Rightarrow$$ better response to chemotherapy

- **Astrocytomas**
  - Secondary Astrocytomas
    - Low grade $$$\Rightarrow$$ grade 3 (AA) $$\Rightarrow$$ GMB
    - LOH p16, LOH 22q, TDPDF $$\Rightarrow$$ CDK4 amp, LOH Rb, LOH Ch9 p15q16, 10q
  - Primary Astrocytomas
    - Precursor $$\Rightarrow$$ GMB
    - MDM2 amp, EGFR amp, LOH 10 (PTEN)

Sources: www.UpToDate.com / Peer-reviewed Literature
Example of Neuropathology Molecular Work Up

- FISH
  - 1p
  - 19q
  - EGFR
  - p16
- Microsatellite Analysis by PCR
  - 1p
  - 19q
  - 9p (CDKN2A/2B, p16)
  - 10q (PTEN)
  - 17p (p53)
- Immunohistochemistry
  - EGFR
  - p53
  - Ki-67 proliferation index

Slide courtesy of Jill Hagenkord, MD, Creighton Medical Labs.

Oligodendroglioma Dx: 1p/19q loss

Data from The Methodist Hospital, Houston, TX.

Oligodendroglioma?

This doesn't look like an oligodendroglioma at all...

Let's look more closely at Chr 9 for OD 510...

Copy loss LOH  Copy neutral LOH  Homozygous deletion

This is probably a high grade astrocytoma.

Only SNP array virtual karyotype would detect all the lesions on 9p.

Slide courtesy of Jill Hagenkord, MD, Creighton Medical Labs.
The tumor above is called ASTROCYTOMA GRADE 3, which implies that it is an evolving secondary tumor on its way to becoming a GBM. The virtual karyotype indicates that this is a primary GBM, instead. Since this is a GBM, studies have shown:

- EGFR amp → good prognosis, eligibility for EGFR inhibitors
- MDM2 amp → poor prognosis

The tumor below is also diagnosed as an ASTROCYTOMA GRADE 3, but this patient has a poor prognosis and is not eligible for EGFR inhibitors/drug trials. The loss of PTEN and the RB pathway abnormalities are associated with a shorter survival time.

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**Childhood Cancers**

**Prognosis in Neuroblastoma**

- Overall genomic pattern is a predictor of outcome
- Whole chromosome copy number changes are associated with excellent survival.
- Any kind of segmental chromosome copy number changes are associated with a high risk of relapse.
- Additional independent predictors of decreased overall survival are MYCN amplification, 1p and 11q deletions, and 1q gain.

Childhood Cancers

- Medulloblastoma
  - Array-based karyotyping of 260 medulloblastomas identified clinical subgroups based on cytogenetic profiles:
    - Poor prognosis: gain of 6q or amplification of MYC or MYCN
    - Intermediate: gain of 17q or an i(17q) without gain of 6q or amplification of MYC or MYCN
    - Excellent prognosis: 6q and 17q balanced or 6q deletion

Prognostic Classification of Wilms tumor
- Large clinical trials have identified loss of 1p and 16q (with LOH) as markers for Wilms tumor patients who have a significantly increased risk of relapse and death.

Other Applications
- Other Cancers
  - Colon Cancer (18q LOH / EGFR amplification / MMR gene deletions)
  - Uveal Melanoma (Monosomy 3)
  - Breast (ERBB2 [Her2Neu] amplification)
  - Pancreas (BRCA mutation carriers) Chromosome 13 LOH

  Companion Diagnostics / Drug Eligibility
  - Her2 amplification
  - EGFR amplification

Colorectal Cancer
- 18q LOH is an established biomarker associated with high risk of tumor recurrence in stage II colon cancer.
- Colorectal cancers are classified into specific tumor phenotypes based on molecular profiles:
  - Chromosomal instability (CIN) which have allelic imbalance at a number of chromosomal loci, including 5q, 8p, 17p, and 18q.
  - Microsatellite instability (MSI) which tend to have optical karyotypes.
Melanoma

Uveal Melanoma

- Monosomy 3 is associated with poor prognosis in uveal melanoma, which is strongly correlated with metastatic spread.
- Gains on chromosomes 6 and 8 are often used to refine the predictive value of the Monosomy 3 screen, with gain of 6p indicating a better prognosis and gain of 8q indicating a worse prognosis in tumors diploid for chromosome 3.
- Isodisomy 3 (e.g., aUPD) is prognostically equivalent to monosomy 3.


Quote: “An important advantage of SNP is its ability to detect isodisomy 3. Indeed, all three false-negatives calls by aCGH were due to isodisomy. Importantly, isodisomy 3 carries the same prognostic significance as monosomy 3 but is not detected by FISH, CGH, and other techniques that count the number of chromosomes.”

Drug Eligibility and Companion Diagnostics

- Her2neu amplification and Herceptin
- EGFR amplification and TKI’s (e.g., Erbitux, Tarceva/Iressa)
- 13q LOH and PARP inhibitors

Slide courtesy of Jill Hagenkord, MD, Creighton Medical Labs

Conclusions

- SNP arrays are a powerful tool for whole genome analysis of chromosomal lesions in human tumors (virtual karyotyping).
- Virtual karyotyping can see chromosomal imbalances and UPD at the same time
  - Unable to detect translocations*, and overall ploidy
- Virtual karyotyping with SNP arrays can be used to detect clinically relevant genomic lesions in human tumors
  - Ability to use fresh and FFPE tumor samples
  - Might replace FISH panels (CLL, MDS, kidney tumors)
  - Can complement other studies (MSI, mutation analysis, translocation assays)
Acknowledgements

Methodist

Creighton

UPMC

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- GU Pathology at UPMC - Anil Parwani MD, PhD, Sheldon Bastacky MD & Rajiv Dhir MD
- Jeff Chang MD PhD, Methodist
- Bob Amato DO, Univ of Texas – Memorial Hermann
- Eric Jonasch MD, MD Anderson Cancer Center
- Zoran Gatalica MD & Shera K Kahn, PhD – Creighton, Julia Bridge MD – U of Nebraska

Questions?


Bibliography

SNP Arrays

Renal Cell Tumors
Bibliography (cont.)

Renal Cell Tumors (cont’d)


Molecular Neuropathology


Molecular Hematopathology


Childhood Tumors


Reproducibility

- 37 samples were run up to 4 times, with all repeats from each sample producing identical virtual karyotypes
- 250K arrays showed better resolution for lesion boundaries and smaller gain/losses.
- LOH detection by the Hidden Markov Model was best with the 10K arrays
- 3 samples that failed on the 10K platform, produced successful results on the 250K microarrays.
We observed heterogeneity in 1 out of 5 samples (20%) when different tumor regions obtained from the same paraffin block.

Genetic tumor heterogeneity was found to be 57% (4/7) more frequent when two or more different blocks from the same specimen were analyzed.

In 6 renal tumor samples, we compared tumor areas with and without sarcomatoid transformation; in 5 of 6 cases (83%), the sarcomatoid portion showed additional chromosomal imbalances compared to the non-sarcomatoid areas.

**Comparison with Cytogenetics**

19 cases with conventional cytogenetics (CG and V-karyotype)

- Identifying disease-defining lesions
  - V-karyotype: 19/19
  - CG: 15/19
  - Platforms agreed in 15/15
- Comparison metrics
  - Did the final diagnoses agree? • YES 15/15
  - Did the karyotypes agree? • Not always
    - Completely (C): 8/19
    - Partially (P): 8/19, those with composite karyotypes
    - No agreement (N): 3/19 – CG showed normal karyotype – likely cultured normal stroma


Slide courtesy of Jill Hagenkord, MD, Creighton Medical Labs
Acquired UPD is very common event in certain human tumors

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Percentage</th>
<th>Source(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glioblastomas</td>
<td>18/22</td>
<td>Neuro Oncol. 2008 Aug 12</td>
</tr>
<tr>
<td>MAP carcinomas</td>
<td>71%</td>
<td>J. Pathol. 2008 Sep;216(1):25-31</td>
</tr>
<tr>
<td>Follicular lymphoma</td>
<td>50%</td>
<td>Clin Cancer Res. 2007 Aug 14;17(16):4776-81</td>
</tr>
<tr>
<td>Medulloblastoma</td>
<td>17/42</td>
<td>Genes Chrom Cancer 2006 Jan;45(1):47-60</td>
</tr>
<tr>
<td>Cervical cancer</td>
<td>75%</td>
<td>BMC Genomics. Feb 2007</td>
</tr>
</tbody>
</table>

Rate of copy neutral LOH depends on what cancer type, sample type, testing platform, algorithms, and thresholds you use.

Some reported copy neutral LOH may be genuine rather than acquired UPD in tumor cells.

Rate of copy neutral LOH depends on what cancer type, sample type, testing platform, algorithms, and thresholds you use.

Some reported copy neutral LOH may be genuine rather than acquired UPD in tumor cells.

Not all copy neutral LOH is clinically relevant (nor are all deletions).

Some copy neutral LOH is clinically relevant and can be the biological equivalent of a deletion.

Therefore, an integrative analysis of LOH and copy number changes is imperative in cancer applications.