Session 7:
Genetics Revealing the Biology of Acute Leukemias

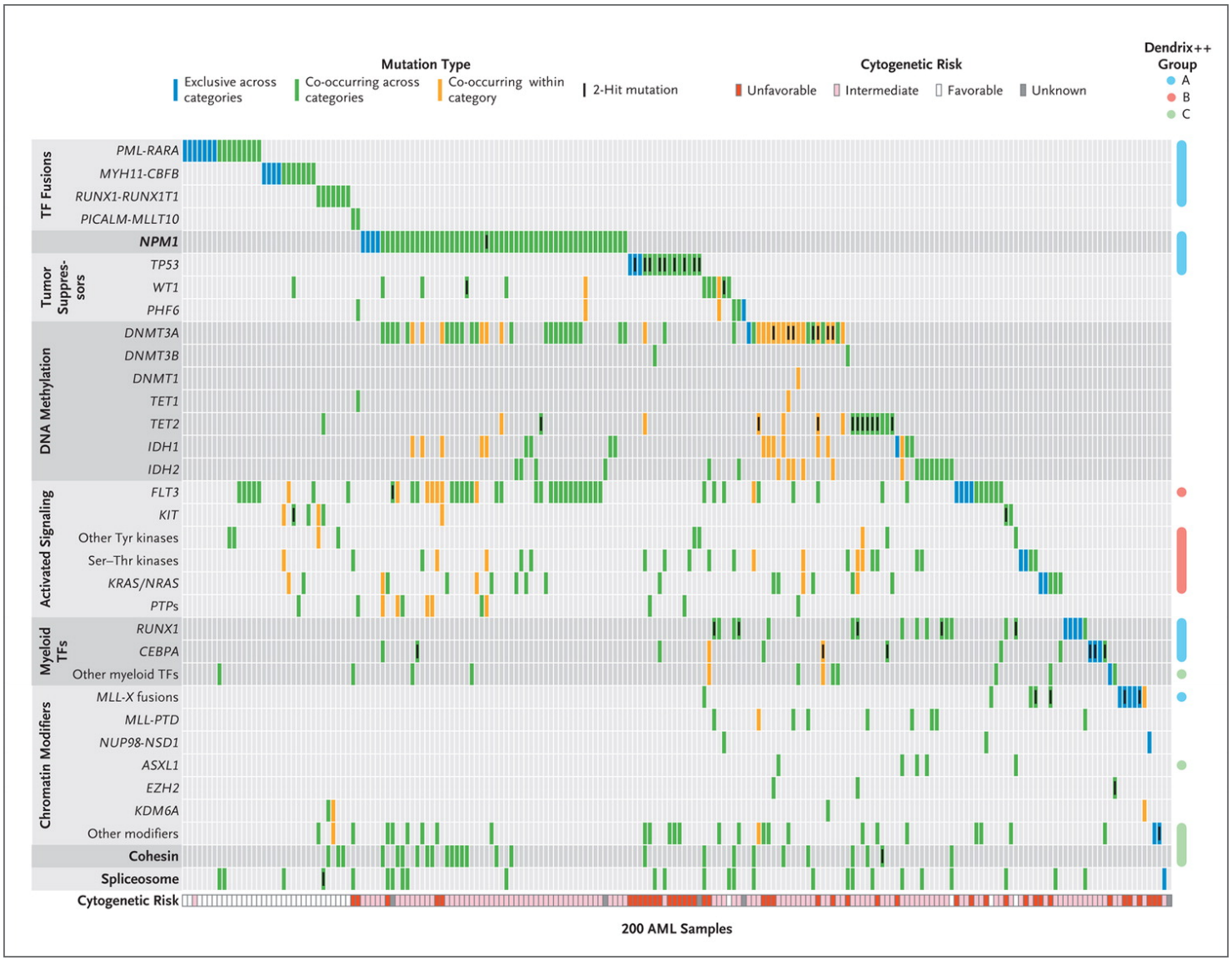
Chairs:

Magdalena Czader, MD, PhD

David Czuchlewski, MD

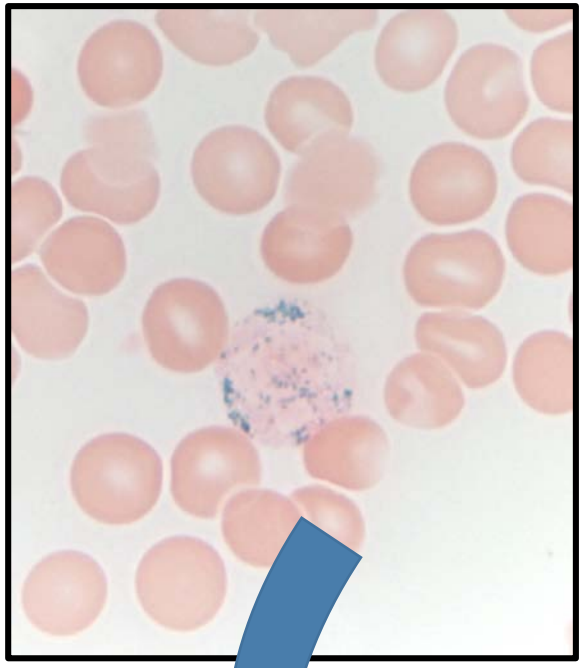
8:30 am – 8:40 am	**Session Introduction**
8:40 am – 9:55 am	**Case Presentations**
9:55 am – 10:15 am	**Session Summary**

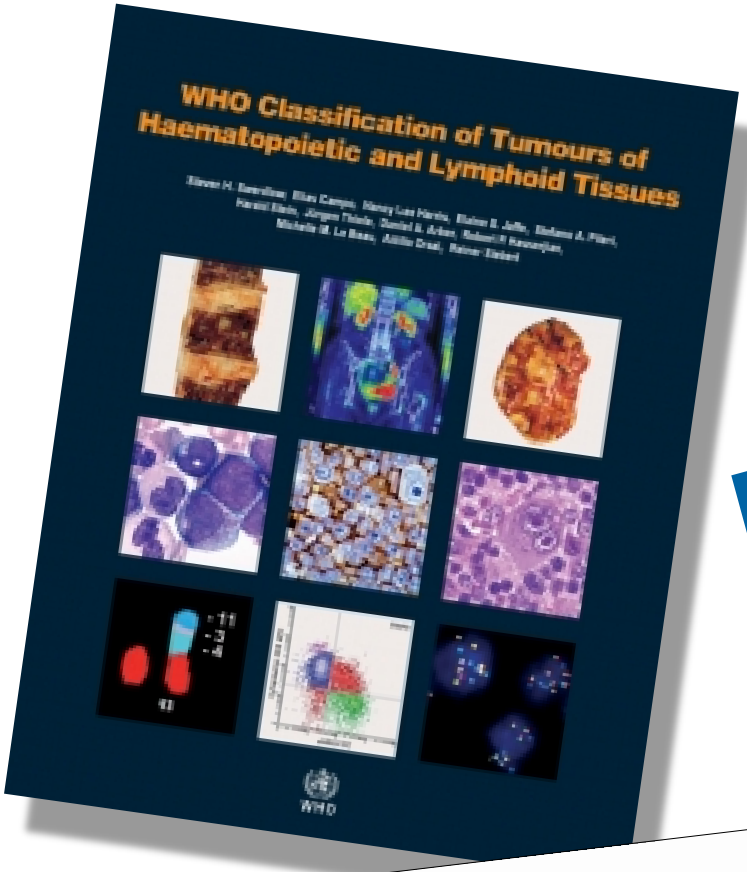
Genomic landscape, *de novo* adult acute myeloid leukemia, The Cancer Genome Atlas Research Network, 2013



N Engl J Med 2013; 368:2059-2074

New landscapes, SH/EAHP Workshop Session 7, 2017





NCCN

ELN European LeukemiaNet

Initial Diagnostic Workup of Acute Leukemia

Guideline From the College of American Pathologists and the American Society of Hematology

niel A. Arber, MD; Michael J. Borowitz, MD, PhD; Melissa Cessna, MD; Joan Etzell, MD; Kathryn Foucar, MD;
obert P. Hasserjian, MD; J. Douglas Rizzo, MD; Karl Theil, MD, PhD; Sa A. Wang, MD; Anthony T. Smith, MLS;
R. Bryan Rumble, MSc; Nicole E. Thomas, MPH, CT(ASCP)^{cm}; James W. Vardiman, MD

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2017
Acute Myeloid Leukemia

RISK STATUS BASED ON VALIDATED CYTOGENETICS AND MOLECULAR ABNORMALITIES[1]

RISK STATUS	CYTOGENETICS	MOLECULAR ABNORMALITIES
Favorable-risk	Core binding factor: inv(16)[2,3,4] or t(16;16)[2,3,4] or t(8;21)[2,4] or t(15;17)[4]	Normal cytogenetics: NPM1 mutation in the absence of FLT3-ITD or isolated biallelic (double) CEBPA mutation
Intermediate-risk	Normal cytogenetics +8 alone t(9;11) Other non-defined	Core binding factor with KIT mutation[2]
Poor-risk	Complex (≥3 clonal chromosomal abnormalities) Monosomal karyotype -5, 5q-, -7, 7q- 11q23 - non t(9;11) inv(3), t(3;3) t(6;9) t(9;22)[5]	Normal cytogenetics: with FLT3-ITD mutation[6] TP53 mutation

2017 European LeukemiaNet AML risk stratification by genetics

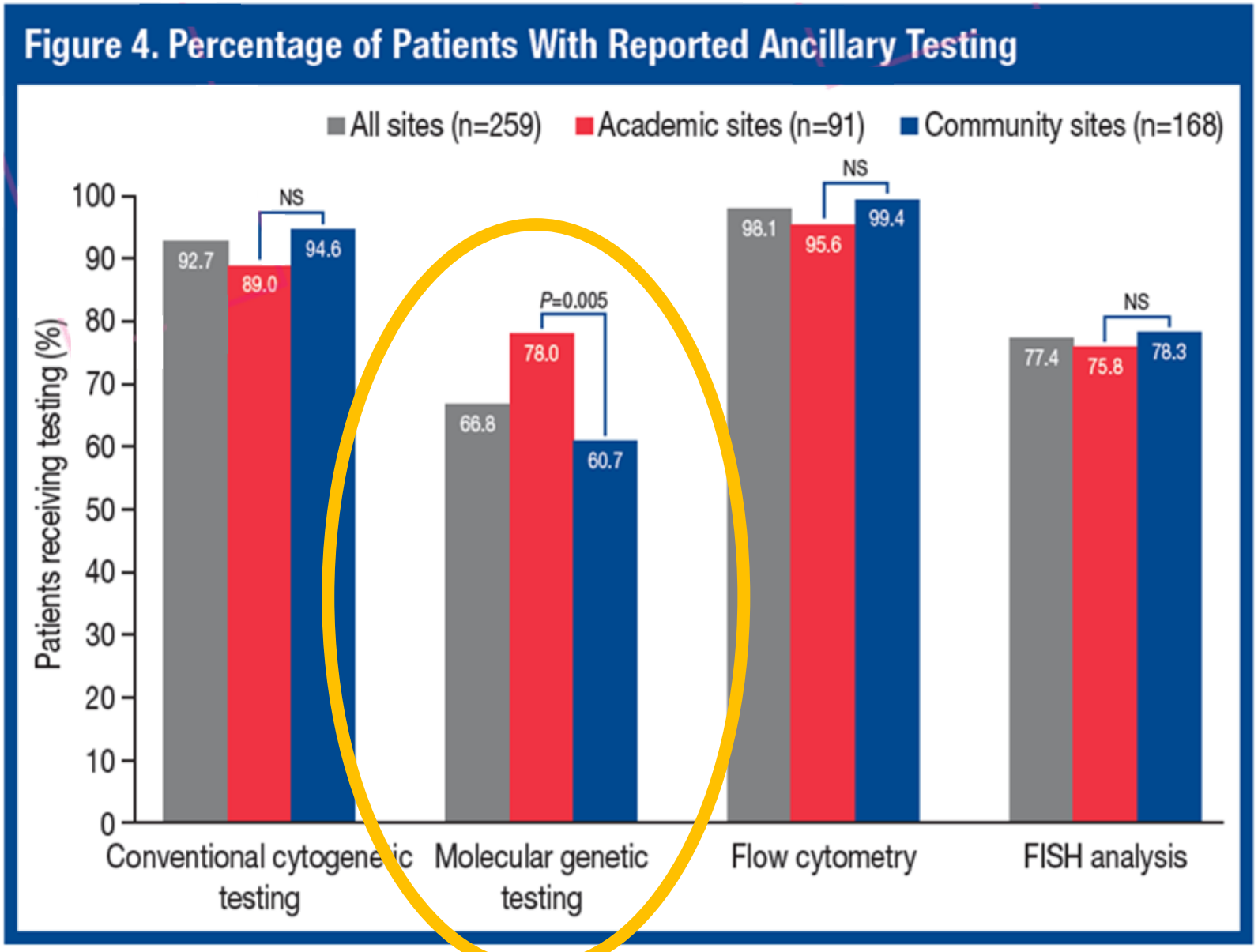
Favorable	**t(8;21)(q22;q22.1); *RUNX1-RUNX1T1***
	inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*
	Mutated *NPM1* without *FLT3*-ITD or with *FLT3*-ITD low (AR <0.5)
	Biallelic mutated *CEBPA*
Intermediate	**Mutated *NPM1* and *FLT3*-ITD high (AR ≥0.5)**
	Wild type *NPM1* without *FLT3*-ITD or with *FLT3*-ITD low (AR <0.5) (w/o adverse-risk genetic lesions)
	t(9;11)(p21.3;q23.3); *MLLT3-KMT2A* (takes precedence over rare, concurrent adverse-risk gene mutations)
	Cytogenetic abnormalities not classified as favorable or adverse
Adverse	**t(6;9)(p23;q34.1); *DEK-NUP214***
	t(v;11q23.3); *KMT2A* rearranged
	t(9;22)(q34.1;q11.2); *BCR-ABL1*
	inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2,MECOM(EVI1)*
	-5 or del(5q); -7; -17/abn(17p)
	Complex karyotype, monosomal karyotype
	Wild type *NPM1* and *FLT3*-ITD high (AR≥0.5)
	Mutated *RUNX1* (unless co-occurring in favorable-risk AML)
	Mutated *ASXL1* (unless co-occurring in favorable-risk AML)
	Mutated *TP53*

Dohner H et al. 2017 PMID: 27895058

Molecular testing recommended by CAP/ASH Guideline for Initial Diagnostic Workup of Acute Leukemia

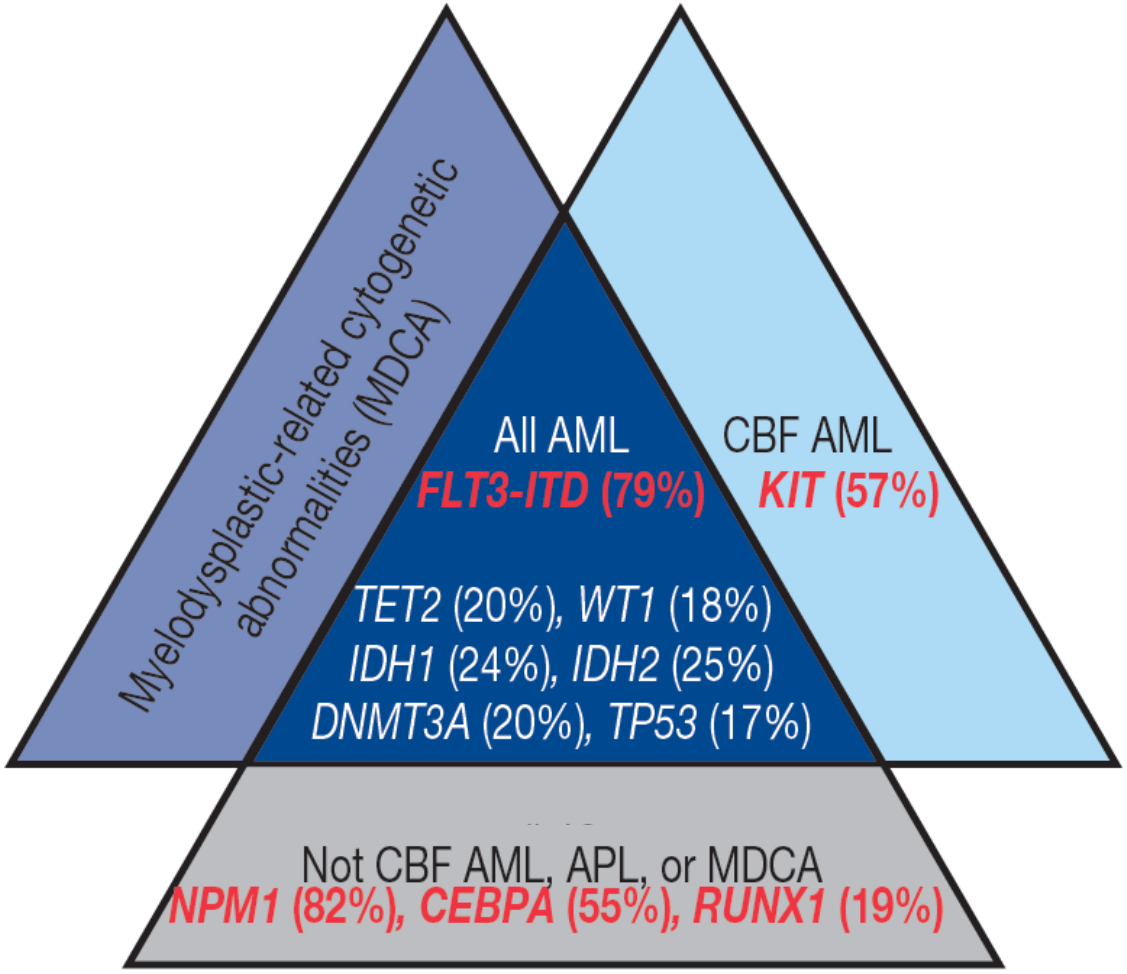
Type of acute leukemia	Recommendation	Strength
Pediatric B-ALL	**Should t(12;21)*ETV6-RUNX1*, t(9;22)*BCR-ABL1*, *KMT2A*, iAMP21, trisomy 4 and 10**	Strong
Adult B-ALL	**Should t(9;22)*BCR-ABL1***	Strong
	May *KMT2A*	Recommended
Any B-ALL	May *PAX5*, *JAK1*, *JAK2*, *IKZF1*, *CRLF2*	Recommended
Any T-ALL	May *NOTCH1*, *FBXW7*	Recommended
Any AML	**Should *FLT3*-ITD (including level of mutation)**	Strong
	May include but not limited to *IDH1*, *IDH2*, *TET2*, *WT1*, *DNMT3A*, *TP53*	Recommended
Adult CBF-AML	**Should *KIT***	Strong
Pediatric CBF-AML	May *KIT*	Expert consensus
APL	**Should rapid *PML-RARA***	Strong
AML other than CBF, APL, or myelodysplasia-related cytogenetics	**Should *NPM1*, *CEBPA*, *RUNX1***	Strong
MPAL	**Should t(9;22)*BCR-ABL1*, *KMT2A***	Strong

Arber DA et al. 2017 PMID:28225303



George TI et al. Antecedent Conformity of Diagnostic and Molecular Testing Patterns in Clinical Practice for Newly Diagnosed Acute Myeloid Leukemia With American Society of Hematology and College of American Pathologists Guidelines. Presented at ASCP 9/8/17

Molecular testing performed in practice (vs. CAP/ASH Guidelines)



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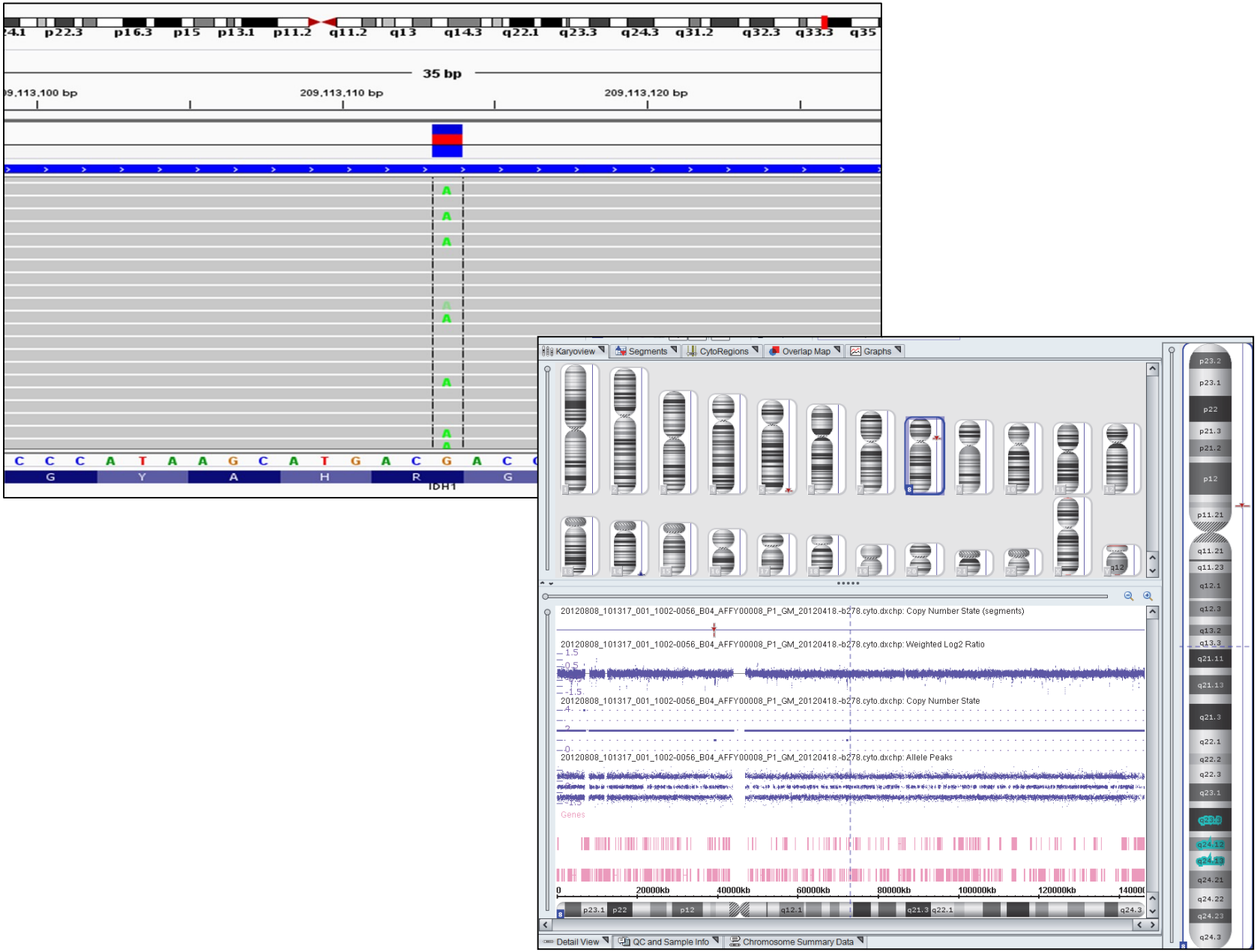
35 bp
209,113,100 bp
209,113,110 bp
209,113,120 bp
C C C A T A A G C A T G A C G A C
G Y A H R G
IDH1
Karyoview
Segments
CytoRegions
Overlap Map
Graphs
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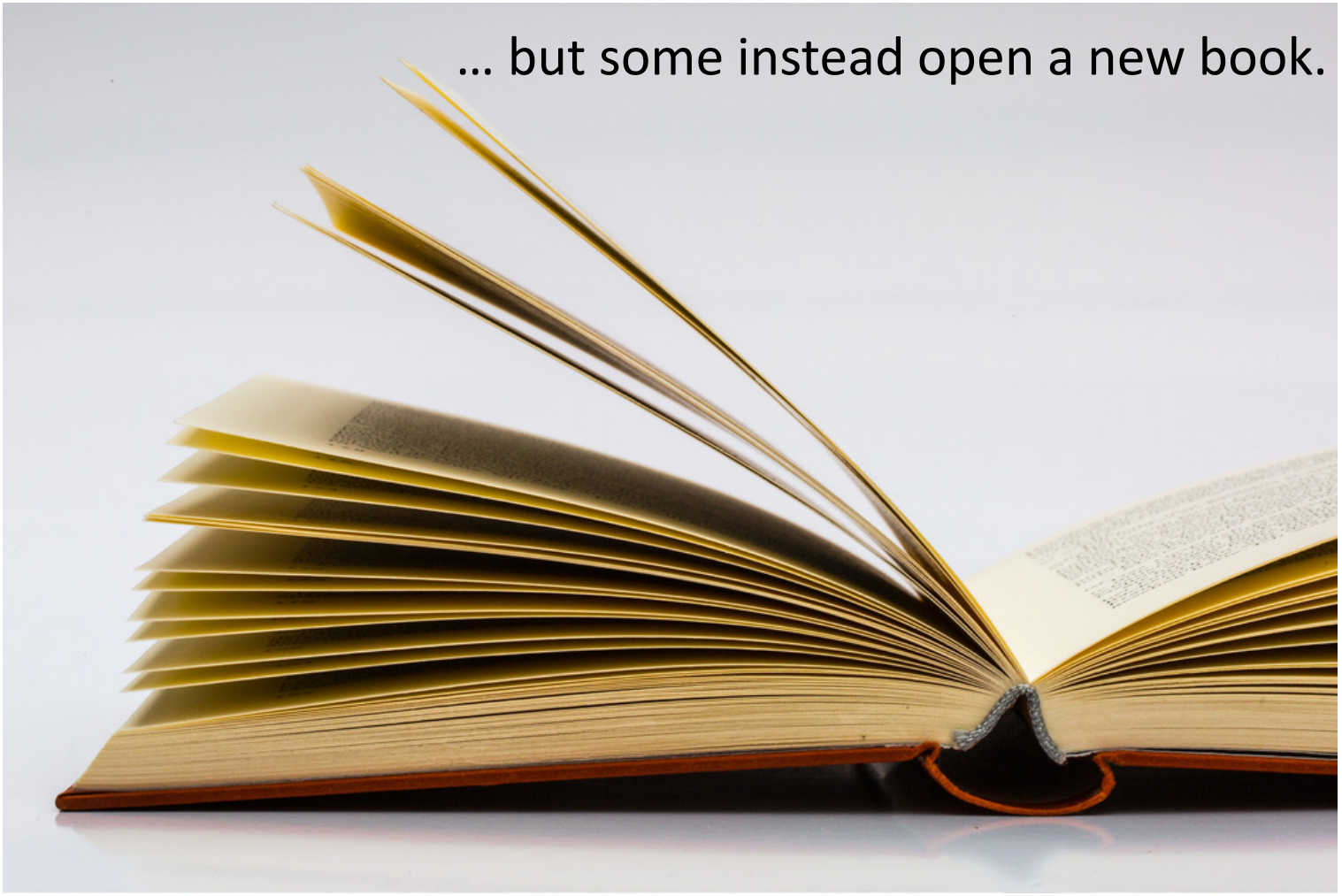
Genes
Detail View
QC and Sample Info
Chromosome Summary Data

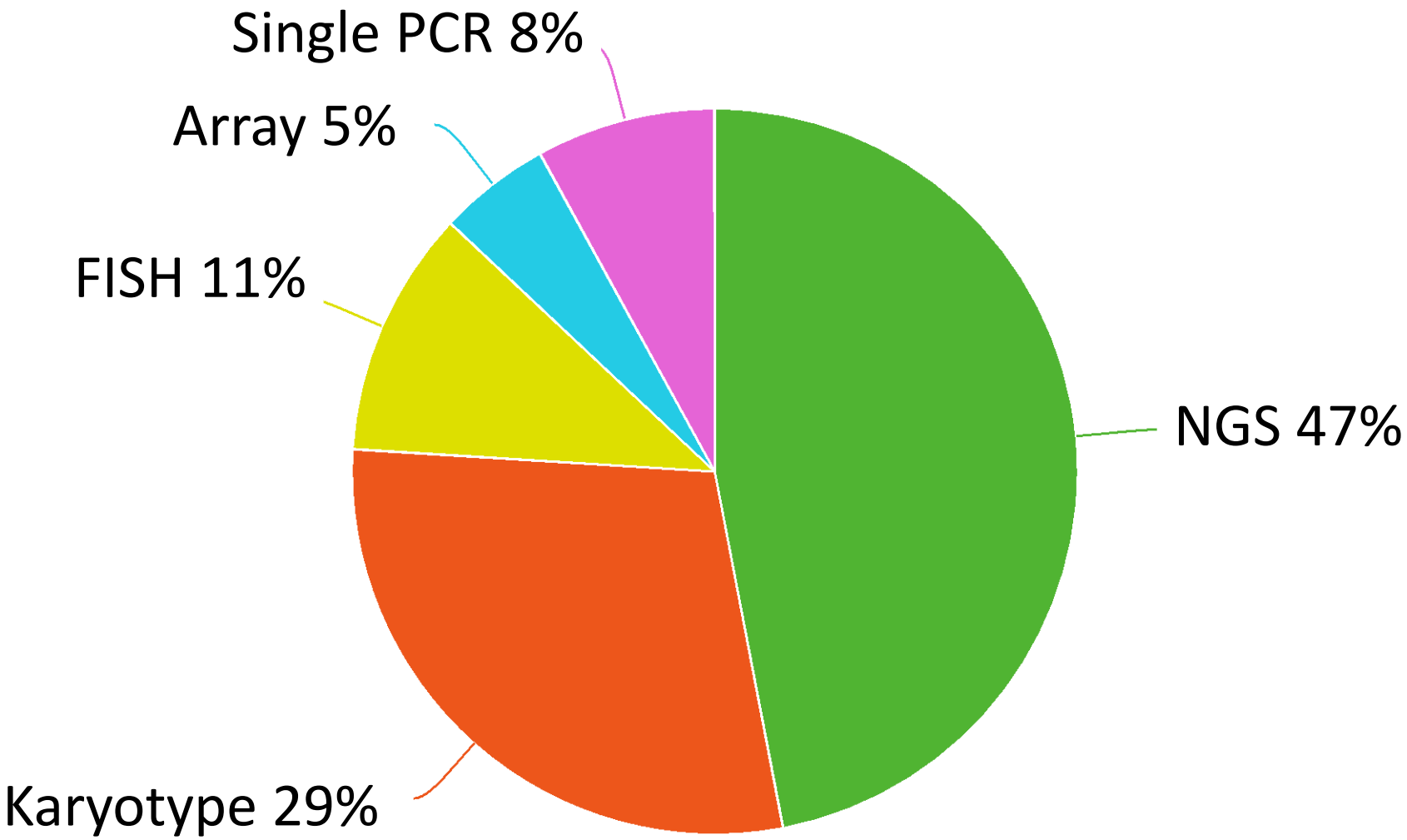
Most genetic findings in acute leukemias “close a chapter”…



Types of acute leukemia cases in this session

- De novo acute leukemias and therapy-related myeloid/lymphoid neoplasms with unusual genetic features
- Genetic abnormalities indicating residual disease or underlying hematopoietic neoplasms
- Clonal relationships, clonal evolution, and disease heterogeneity
- Treatment: therapeutic targets and response patterns
- Prognostic implications
- Diagnostic dilemmas

How were the key genetic findings identified in these cases?



Outlier genetic results in acute leukemias: key practical questions

- Is there an alternative diagnosis to consider?
- Does the result alter the WHO 2016 subclassification?
- Does the result suggest something unrecognized in the patient's history?
- Is there targeted therapy available?
- Does the result change the prognosis?
- How to reconcile changes in genetic findings during follow up?

Session 7:

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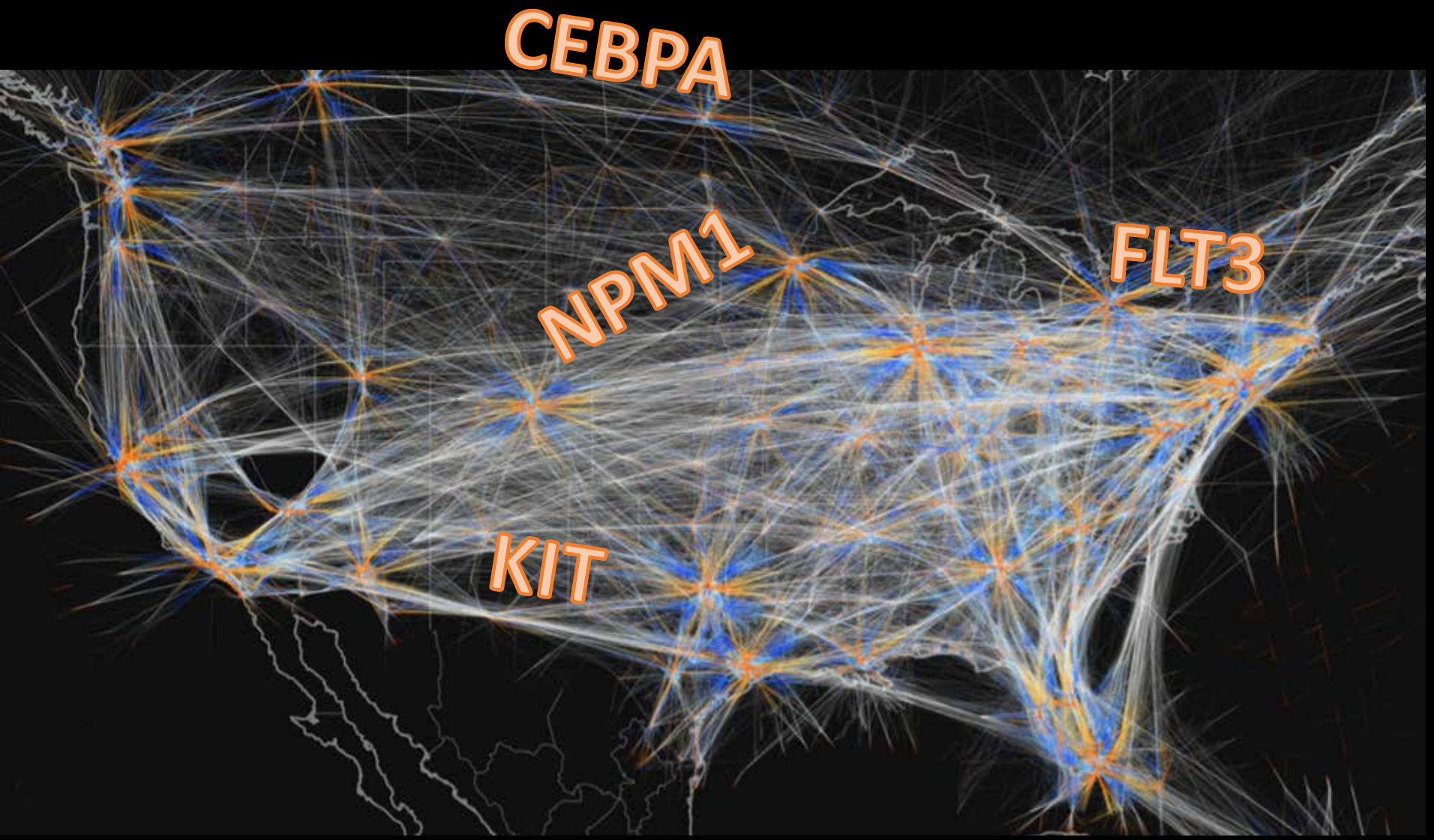
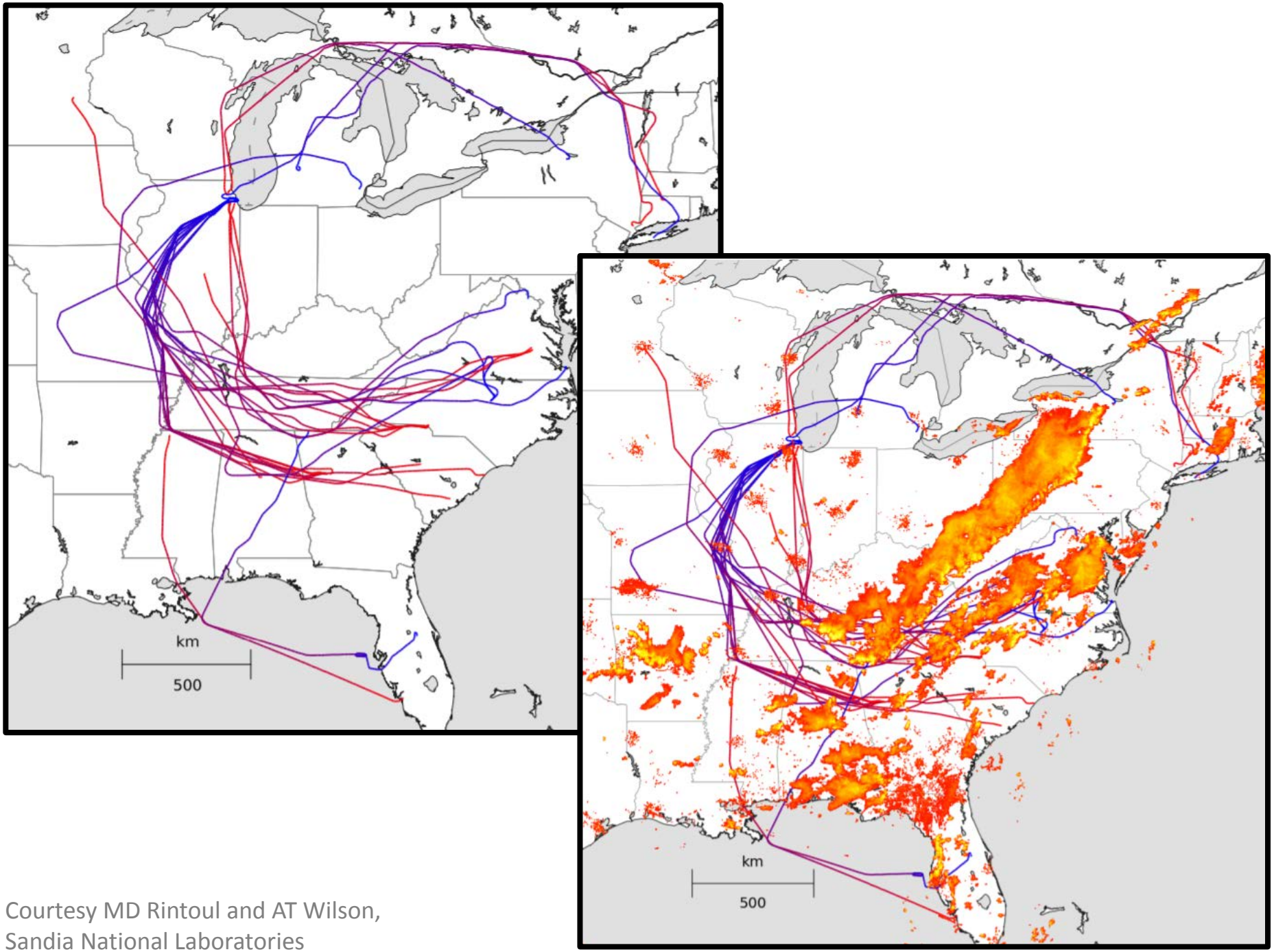
Case 0057	**Jason Aynardi, MD**
Case 0094	**Jessica Snider, MD**
Case 0144	**Siddharth Bhattacharyya, MD**
Case 0119	**Sarah M. Choi, MD PhD**
Case 0148	**Madhu M. Ouseph, MD PhD**
Case 0203	**Rebecca Leeman-Neill, MD PhD**



Courtesy MD Rintoul and AT Wilson, Sandia National Laboratories



Courtesy MD Rintoul and AT Wilson,
Sandia National Laboratories

Hudson River School landscape, Frederic Edwin Church, 1859