Session 8

Genetics Revealing the Biology of Lymphoid Neoplasms

Summary and Conclusions

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Session 8: Themes and Concepts

- "Low grade" lymphoid neoplasms with genetic events associated with "aggressive" biology (5)
- Genetic findings expand the spectrum of disease or support the dia
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- Molecular testing revealed relationship between 2 distinct neoplastic populations (2)
- Genetic events corroborate cell of origin and pathogenetic mechanism and conn tribute to diagnosis (5)

Panoply of Perplexing.. Paralyzing... cases

“Low grade” lymphoid neoplasms with genetic events associated with “aggressive biology”

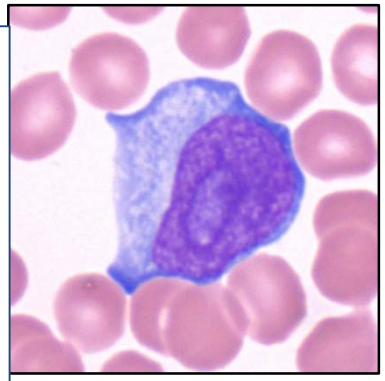
SH2017-0036 **Bryan Rea** Vania Aikawa, Adam Ba University of Pennsylva	Chronic lymphocytic leukemia (with
SH2017-0245 **Kedar Inamdar** Nadhu Menon, Kristin H Juan Gomez-Gelvez Henry Ford Health Syst	
SH2017-0129 **Gabriel Caponetti** Dattatreya M. Phadke, Adam Bagg,MD University of Pennsylva	
SH2017-0261 **Carlos Santonja** Socorro-Maria Rodrigu Rocio-Nieves Salgado S Jorge Polo Jos-Luis Lopez-Lorenzo Fundacion Jimenez Diaz	Follicular lymphoma, grade 1-2 of 3 (with *BCL2* and *BCL6* rearrangements)
SH2017-0358 **Annapurna Saksena** Russell Higgins University of Texas Health San Antonio	Follicular lymphoma, grade 1-2 of 3 (with *MYC* and *BCL2* rearrangements)

Key points

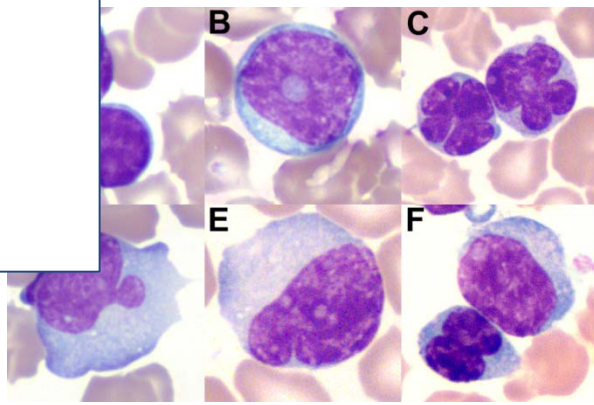
Karyotype alone may be misleading

Genetics may support aggressive biology

Case 36



Case 245



"Low grade" lymphoid neoplasms with genetic events associated with "aggressive biology"

SH2017-0036 **Bryan Rea** Vania Aikawa, Adam Bagg University of Pennsylvania	Chronic lymphocytic leukemia (with t(8;14)) subsequent FISH studies did not show *IGH/MYC*
SH2017-0245 **Kedar Inamdar** Nadhu Menon, Kristin Karner and Juan Gomez-Gelvez Henry Ford Health System	CLL with t(14;19] involving *BCL3*
SH2017-0129 **Gabriel Caponetti** Dattatreya M. Phadke, MD and Adam Bagg,MD University of Pennsylvania	Follicular lymphoma, grade 1-2 of 3 (with *MYC* and *BCL2* rearrangements)
SH2017-0261 **Carlos Santonja** Socorro-Maria Rodriguez-Pinilla Rocio-Nieves Salgado Sínchez Jorge Polo Jos-Luis Lopez-Lorenzo Fundacion Jimenez Diaz	Follicular lymphoma, grade 1-2 of 3 (with *BCL2* and *BCL6* rearrangements)
SH2017-0358 **Annapurna Saksena** Russell Higgins University of Texas Health San Antonio	Follicular lymphoma, grade 1-2 of 3 (with *MYC* and *BCL2* rearrangements)

Key points

MYC and *BCL2/BCL6* rearrangement (DHL only relevant in DLBCL)

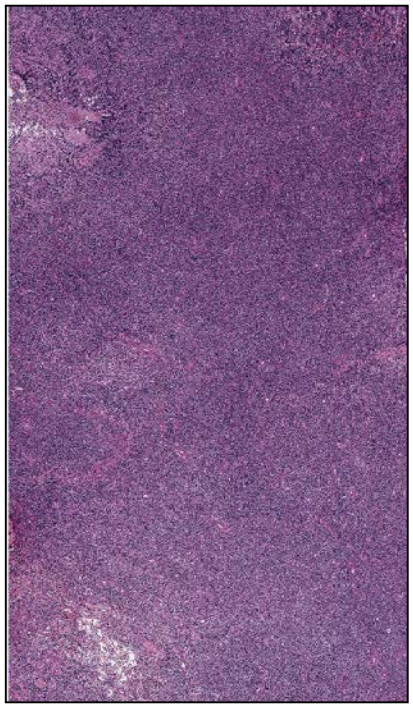
BCL2 and *BCL6* rearrangements do not constitute a DHL

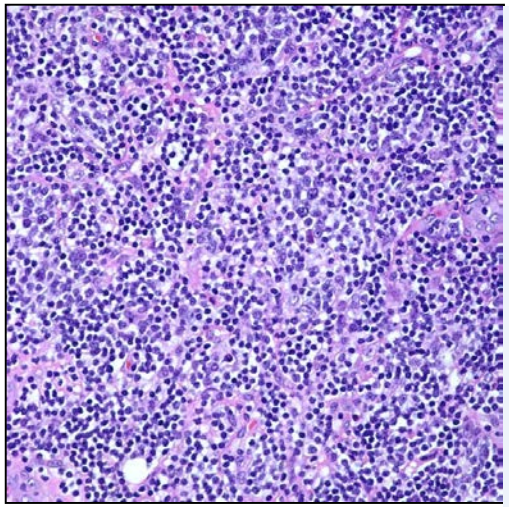
MYC and *BCL2* rearrangement in low grade lymphoma : clinical significance?

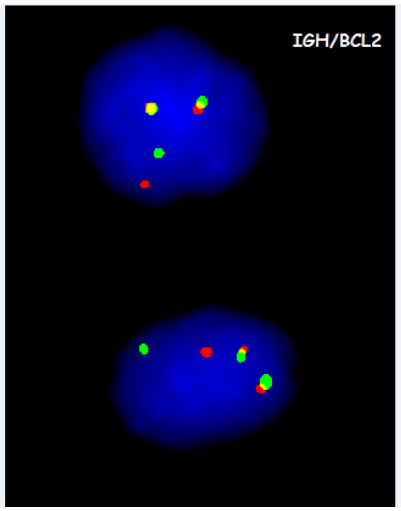
“Low grade” lymphoid neoplasms with genetic events associated with “aggressive biology”

SH2017-0358 **Annapurna Saksena** Russell Higgins University of Texas Health San Antonio	Follicular lymphoma, grade 1-2 of 3 (with *MYC* and *BCL2* rearrangements)

41 Y female

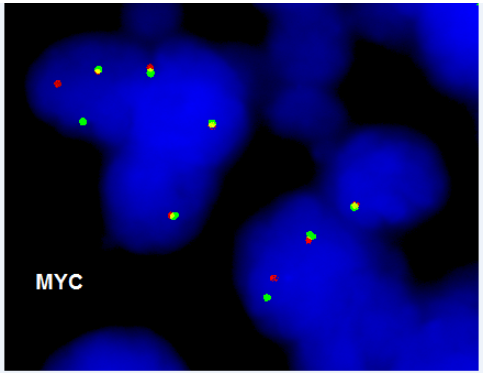


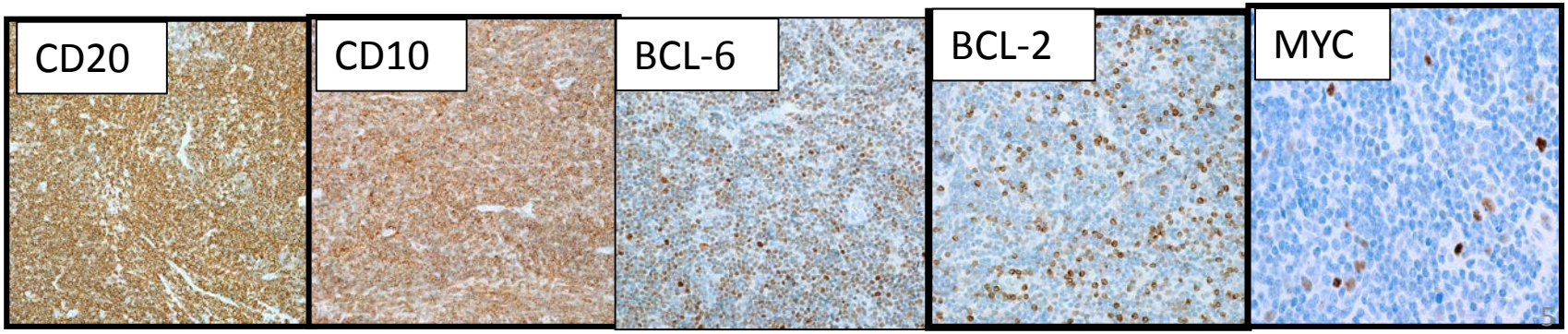




1.5 years later developed DLBCL

FISH: *IGH/BCL2* and *MYC* rearrangement

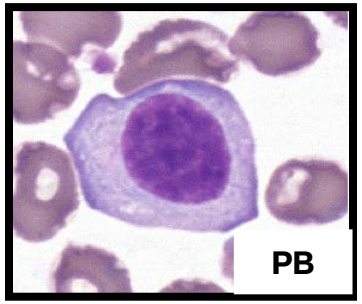


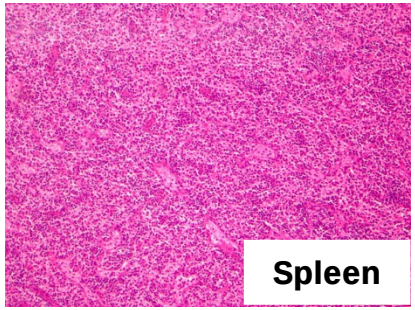


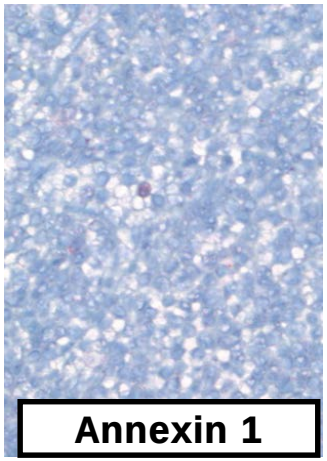
Genetic findings expand the spectrum of disease or support the diagnosis

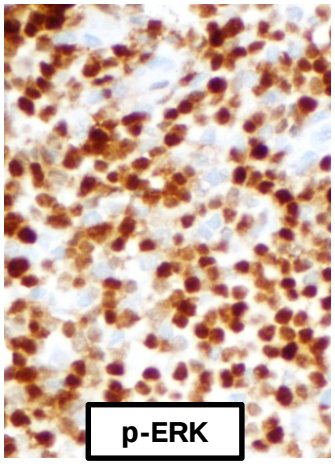
SH2017-0021 **Philipp Raess** Megan O. Nakashima, David Mintzer, Michael Husson, Jennifer J.D. Morrissette, Robert Daber, and Adam Bagg, University of Pennsylvania	Splenic diffuse red pulp small B-cell lymphoma (with *BRAF* mutation)
SH2017-0086 **Leticia Quintanilla-Fend** Institute of Pathology, Tuebingen	Leukemic non-nodal mantle cell lymphoma (with *TP53* mutation)
SH2017-0158 **Katrin Huettl** Alexander Stehle Institut fur Pathologie, Robert-Bosch Krankenhaus Stuttgart	Bone marrow: Classical Hodgkin lymphoma. Liver: PTCL, NOS
SH2017-0193 **Chad Hudson** Janice M. Spence, Paul Rothberg, Hani Katerji, W. Richard Burack University of Rochester	FL, grade 1-2 of 3 (t(14;18) negative]
SH2017-0195 **Allison Wasserman** Austin Turner Vanderbilt University Medical Center	Diffuse large B-cell lymphoma, NOS (with t(9;11))
SH2017-0223 **Simone Davion** Qian-Yun Zhang University of New Mexico	Extranodal NK/T cell lymphoma, nasal type

Case 21







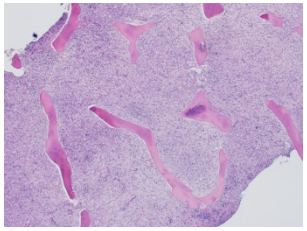


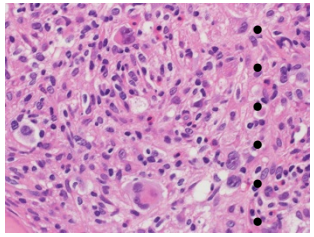
Genetic findings expand the spectrum of disease or support the diagnosis

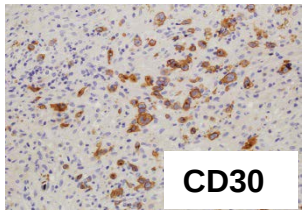
SH2017-0158 **Katrin Huettl** Alexander Stehle Institut fur Pathologie, Robert-Bosch Krankenhaus, Stuttgart	Bone marrow: Classical Hodgkin lymphoma. Liver: PTCL, NOS

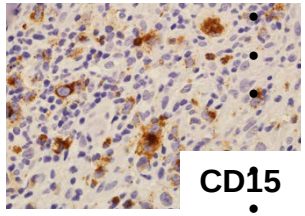
18-year old male splenomegaly, multiple retroperitoneal lymph nodes, weight loss, night sweats, microcytic anemia, and multiple bone lesions.

BM 2013









- CD30+
- CD15+
- CD20-
- PAX5-
- OCT2-, BOB1(+)
- LMP-
- CD3-, CD5-, CD7-
- ALK-
- CD45 (CLA)-
- Granzyme B+
- Perforin(+)

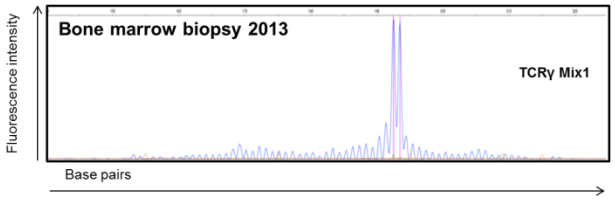
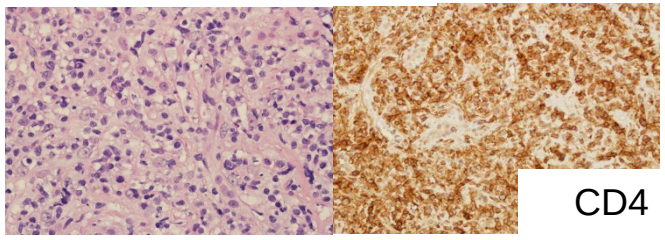
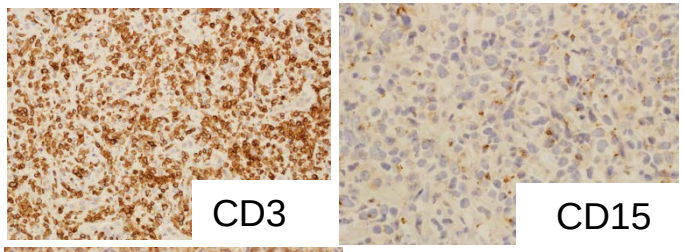
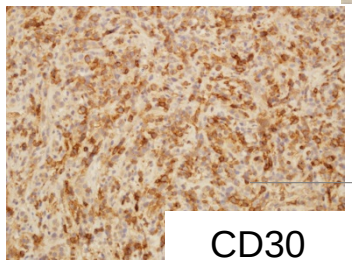


Figure 1: **Fragment analysis (GeneScan) of amplified rearranged TCRγ chain genes**;
Results of PCR amplification (Trainor et al., 1991 Blood) with primer pairs TCRγ Mix1 show a clonal T-cell population (198 bp). A single example of reproducible results from quadruplicate analyses is shown.

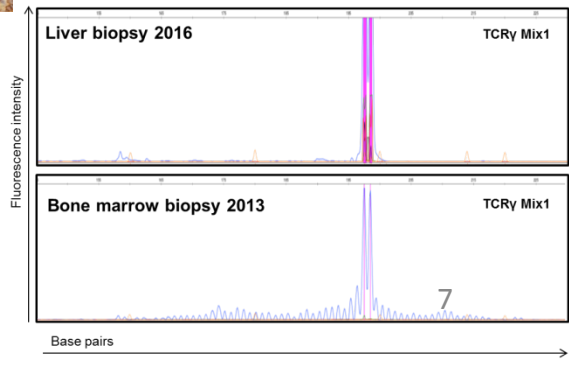
Liver 2016



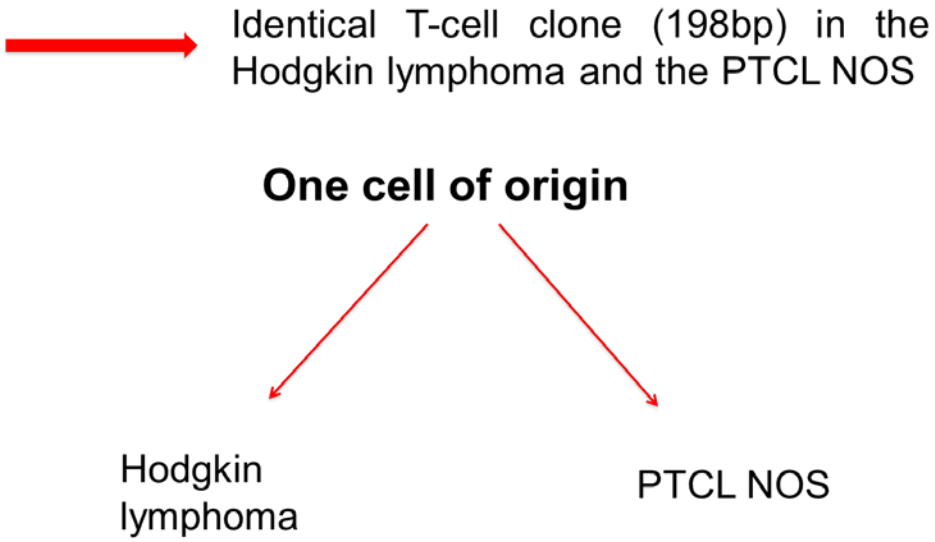




- CD3+, CD4+
- CD5-, CD7-
- CD30+
- CD15-
- Granzyme B (+)
- ALK-
- PAX5-
- Ki67: 50-70%



Molecular results that challenge our existing diagnostic criteria or broaden the spectrum of disease subtypes



Hansmann ML et al., Pathologe; 23(3):207-18 (2002): WHO classification of Hodgkin's lymphoma and its molecular pathological relevance.

CHL with T-cell phenotype and/or T-cell clonality

Müschen M et al., *J Exp Med*.; 191(2):387–394 (2000): Rare occurrence of classical Hodgkin's disease as a T cell lymphoma.

Seitz V et al., *Blood*.; 95(10):3020–3024 (2000): Detection of clonal T-cell receptor gamma-chain gene rearrangements in Reed-Sternberg cells of classic Hodgkin disease.

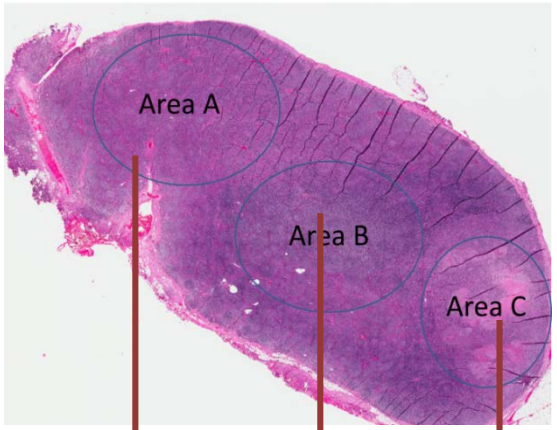
Dirnhofer et al., *Mod Pathol*; 1542-9 (2005): Rare expression of T-cell markers in classical Hodgkin's lymphoma.

Genetic events associated with transformation

SH2017-0085 **Jie Xu** Zhenya Tang, Sa A. Wang, Shaoying Li, L. Jeffrey Medeiros and Guilin Tang MD Anderson Cancer Center	Chronic lymphocytic leukemia with transformation to DLBCL [Richter's transformation, with t(14;19) and t(2;18)
SH2017-0359 **Shiraz Fidai** Sandeep Gurbuxani, Megan M.McNerney, Gordana Raca, Madina Sukhanova, Michael Thirman, John Anastasi, Elizabeth Hyjek University of Chicago	Chronic lymphocytic leukemia with two transformations to DLBCL (Richter's transformation, with *MYC* rearrangements)
SH2017-0141 **James Cook** Cleveland Clinic	Follicular lymphoma, grade 1-2 of 3, with transformation to classical Hodgkin lymphoma (FISH: *BCL2* Rearrangement by BAP) in both
SH2017-0278 **Marsha C. Kinney** University of Texas Health San Antonio	FL grade 3A with transformation to classical Hodgkin lymphoma (FISH: *BCL2* Rearrangement by BAP) in both
SH2017-0227 **Jie Li** April Schrank-Hacker, Mariusz A. Wasik University of Pennsylvania	FL grade 1-2 with transformation to B-ALL/LBL, NOS (BCL2 and BCL6 rearrangement in both, emergence of MYC rearrangement in LBL)
SH2017-0373 **Betty Chung** Reem Alrabeh, Katherine De Filippis, Tara Miller, April Ewton Houston Methodist Hospital	FL, grade 3A, with transformation to B-ALL/LBL, NOS (with *BCL2* and *MYC* rearrangements)

Case 141

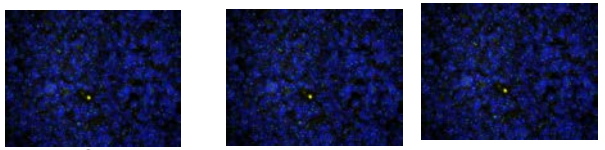
52 Y man with left groin adenopathy



Follicular lymphoma Grade 1/2

Follicular lymphoma Grade 1/2

Classical HL



FISH for BCL2 Break-apart probe +

Genetic events associated with transformation

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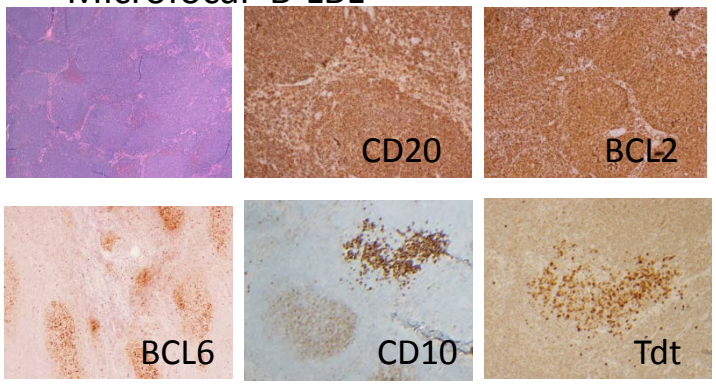
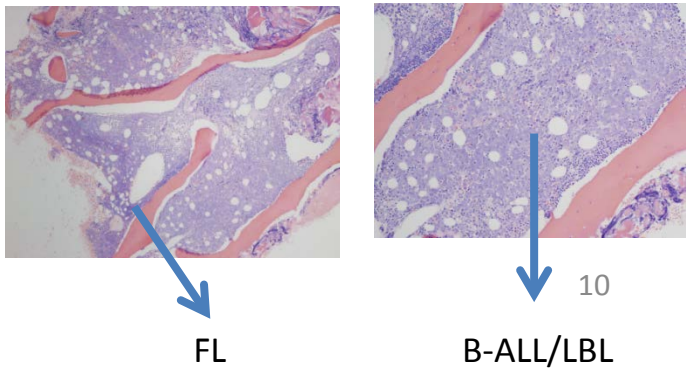
SH2017-0278 **Marsha C. Kinney** University of Texas Health San Antonio	FL grade 3A with transformation to classical Hodgkin lymphoma (FISH: *BCL2* Rearrangement by BAP) in both
SH2017-0227 **Jie Li** April Schrank-Hacker, Mariusz A. Wasik University of Pennsylvania	FL grade 1-2 with transformation to B-ALL/LBL, NOS (BCL2 and BCL6 rearrangement in both, emergence of MYC rearrangement in LBL)
SH2017-0373 **Betty Chung** Reem Alrabeh, Katherine De Filippis, Tara Miller, April Ewton Houston Methodist Hospital	FL, grade 3A, with transformation to B-ALL/LBL, NOS (with *BCL2* and *MYC* rearrangements)

Case 373

- Follicular lymphoma, grade 3A.
- Microfocal B-LBL



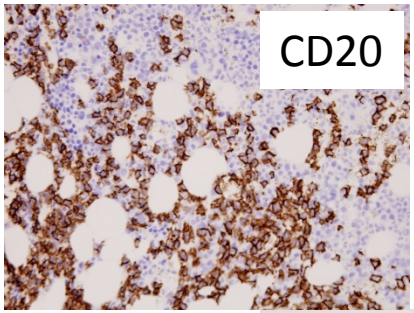
Bone marrow



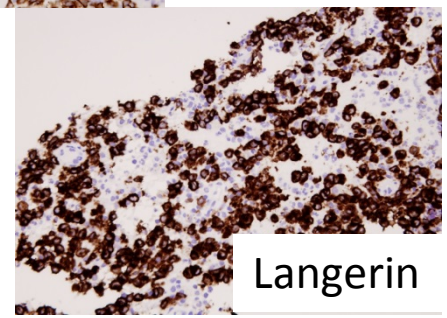
Genetic events associated with lineage switch or lineage plasticity or transdifferentiation

SH2017-0035 **Mariusz Wasik** Q Zhang, HY Wang, A Bogusz, P Zhang, E Orlando, X Liu, S Brooks, E Tomczak, C Watt, J Morissette, SJ Schuster, University of Pennsylvania	Mantle cell lymphoma transdifferentiated to sarcoma
SH2017-0210 **Jonathon Gralewski** Ginell R. Post MD, PhD and Youzhong Yuan MD University of Arkansas	Histiocytic sarcoma (with *IGH-MAF* rearrangement), likely transdifferentiated from plasma cell myeloma (with *IGH-MAF* rearrangement)
SH2017-0246 **Sanam Loghavi** MD Anderson Cancer Center	1. HCL 2. LCH (clonally related?) (BRAF V600E and IGH PCR)
SH2017-0295 **Fina Climent** Rosa Pen├in, Mar Varela, Esmeralda de la Banda, Claudia B Paredes, Eva Domingo, Octavi Servitje, Enric Condom Hospital Universitari de Bellvitge	Langerhans cell sarcoma, transdifferentiated from splenic marginal zone lymphoma (IG gene rearrangement; clonally related)

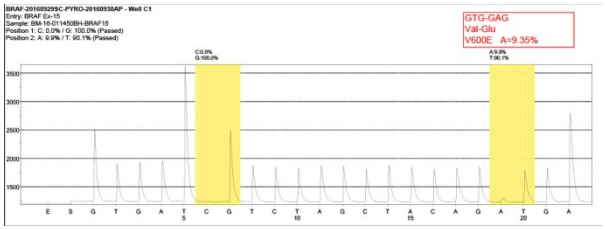
Case 246



HCL



LCH



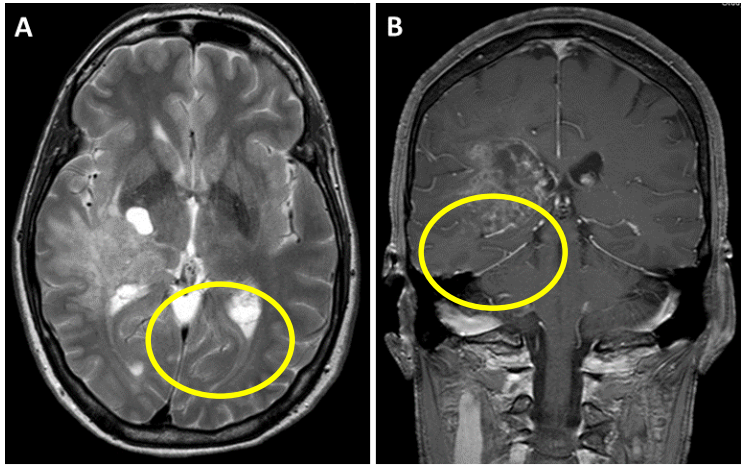
Genetic events with unknown clinical or biologic relevance

Cases: 34, 41, 65,139, 174,213, 365

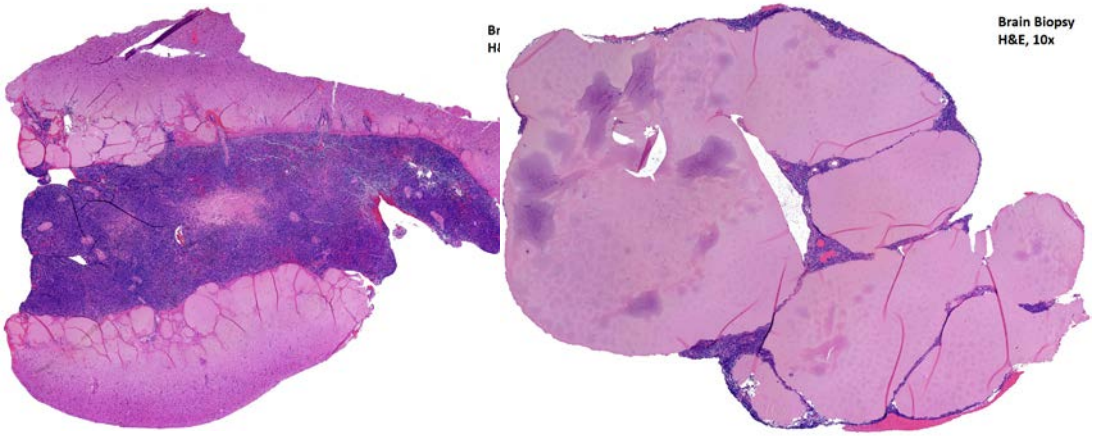
SH2017-0034 **Gabriel Caponetti** University of Pennsylvania	Extranodal marginal zone lymphoma	*ATM, TET2*
SH2017-0041 **Rodolfo Henrich Lobo** University of Arkansas	Chronic lymphocytic leukemia (with t(2;14))	
SH2017-0065 **Jie Xu** L. Jeffrey Medeiros, C. Cameron Yin, Guilin Tang, Pei Lin, and Shaoying Li, MD Anderson Cancer Center	Mantle cell lymphoma, blastoid (with *CCND1*, *MYC*, and *BCL6* rearrangements)	
SH2017-0139 **Shane Betman** Govind Bhagat, M.B.B.S., Mahesh Mansukhani, M.D., Vundavalli Murty, Ph.D., Bachir Alobeid, M.D. Columbia University	B-ALL/LBL, NOS (with *MYC* and *BCL2* rearrangements)	
SH2017-0174 **Agata Bogusz** University of Pennsylvania	Monomorphic post transplant lymphoproliferative disorder, diffuse large B-cell lymphoma type (with *TP53* mutation)	
SH2017-0213 **Siba El**, Vathany Sriganeshan Mount Sinai Medical Center- Miami	Extranodal marginal zone lymphoma	51,XY,+X,del(X)(q27),t(1;14)(q42;q32),+2,add(2)(q11.2),+3.+4,+8,del(8)(q13q22),add(14)(q32),-17,+18,add(22)(p11.2),+mar[cp7]/46,XY[13}
SH2017-0365 **Young-Hyeh Ko**, i-Yeon Hyeon Sungkyunkwan University Samsung Medical Center	Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (with *TP53* mutation)	
Sh-2017-0352 Sophie Song UCLA Medical Center	Intestinal NK cell lymphoma	Negative results

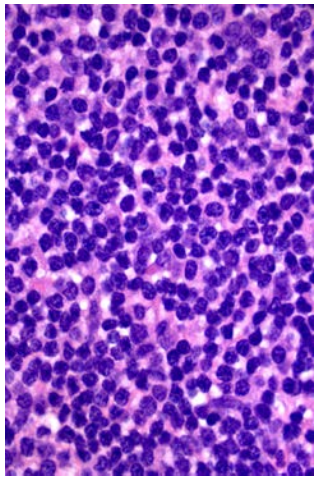
SH2017-0034 **Gabriel Caponetti** University of Pennsylvania	Extranodal marginal zone lymphoma

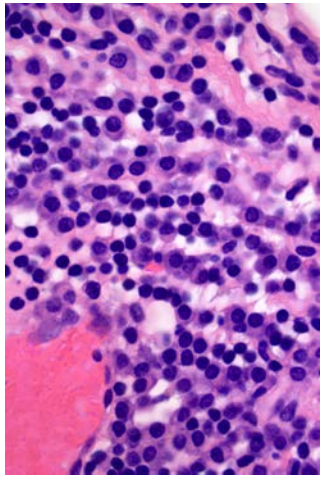
59-year-old female
short episode of expressive aphasia, neurologic symptoms



MRI: extensive abnormal signal in the RIGHT hemisphere involving the RIGHT parietal lobe, RIGHT temporal lobe and RIGHT thalamus.







Brain, right parietal, biopsy:

- Marginal zone lymphoma
- Amorphous eosinophilic aggregates
- LC/MS profile of alpha heavy and kappa light chains

Genetic events with unknown clinical or biologic relevance

SH2017-0034 **Gabriel Caponetti** University of Pennsylvania	Extranodal marginal zone lymphoma

Variants of Uncertain Significance

GENE	PROTEIN CHANGE	cDNA CHANGE
ATM	p.N1356D	c.4066A>G
TET2	p.S689A	c.2065T>G

- A missense variant in ATM at amino acid 1356 converting the wild type residue, Asparagine, to Aspartic Acid in 2678 reads out of a total 5088 sequence reads for an allele frequency of 53%. (Transcript ID NM_000051)
- A missense variant in TET2 at amino acid 689 converting the wild type residue, Serine, to Alanine in 3200 reads out of a total 6725 sequence reads for an allele frequency of 48%. (Transcript ID NM_001127208)

- A rare example of an intraparenchymal primary CNS marginal zone lymphoma
- Monoclonal immunoglobulin deposition disease presenting with CNS aggregomas
- Two variants of uncertain significance involving *ATM* and *TET2* which have not been previously reported in primary CNS low grade B cell lymphomas

Lymphomas with broad heterogeneous morphologic spectrum and genetic results not contributory or difficult to integrate

Cases: 133, 173, 369

SH2017-0133 **Xin Liu** Duke Unviersity	Monomorphic post-transplant lymphoproliferative disorder, large B-cell type, with aberrant T-cell antigen expression	IG Kappa PCR positive TCR PCR negative
SH2017-0173 **Agata Bogusz** University of Pennsylvania	Poorly differentiated malignant neoplasm, possibly large cell lymphoma	Mutations in *TET2, DNMT3A, TP53, MAP2K1.* (VOUS) in ATM (x2), KIT and KRAS
SH2017-0369 **Shanxiang Zhang** Indiana University	Mantle cell lymphoma (with *BCL6* rearrangement)	*CDKN2A* loss in exon 1 and *CDKN2B* loss, *PAX*5 rearrangement involving intron 5, and mutations involving genes *RET*, *BCL10*, *CARD11*, and *CXCR4*.

Molecular testing revealed relationship between 2 distinct neoplastic populations

Cases: 100, 202

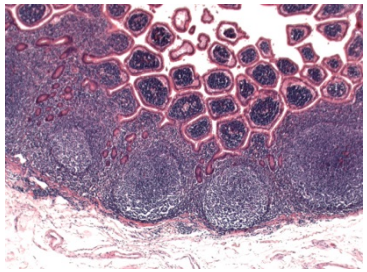
SH2017-0100 **Falko Fend** Institute of Pathology, Tuebingen	Duodenal-type follicular lymphoma with in situ follicular neoplasia-like colonization of abdominal LN germinal centers	*BCL2* rearrangement by FISH Ig K PCR: Clonally related
SH2017-0202 **Chad Hudson** Paul Rothberg, W. Richard Burack University of Rochester	DLBCL, NOS and clonal T-cell lymphoproliferation of uncertain significance	Investigation of recurrence of DLBCL revealed an expected clonal T cell population

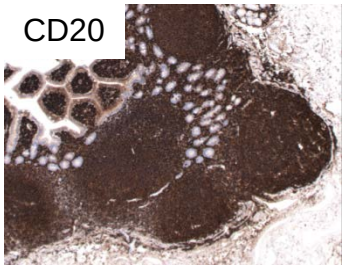
Molecular testing revealed relationship between 2 populations

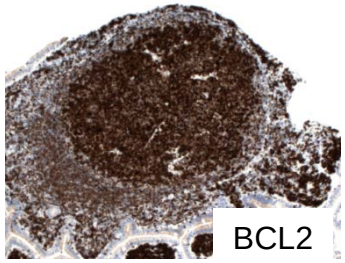
SH2017-0100 **Falko Fend** Institute of Pathology, Tuebingen	Duodenal-type follicular lymphoma with in situ follicular neoplasia-like colonization of abdominal LN germinal centers

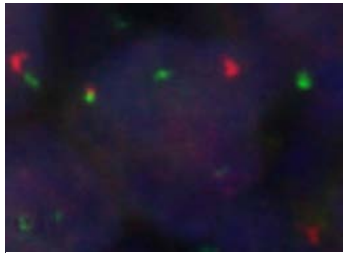
84 Y male

- Whipple's for suspicion of pancreatic Ca
- Irregularities in duodenal mucosa



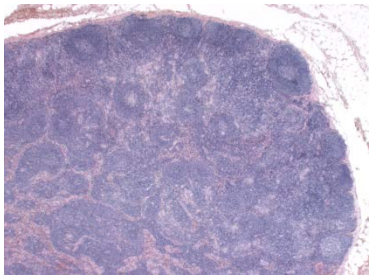


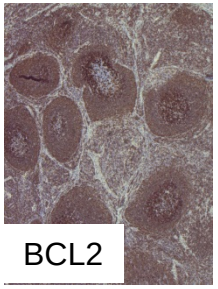




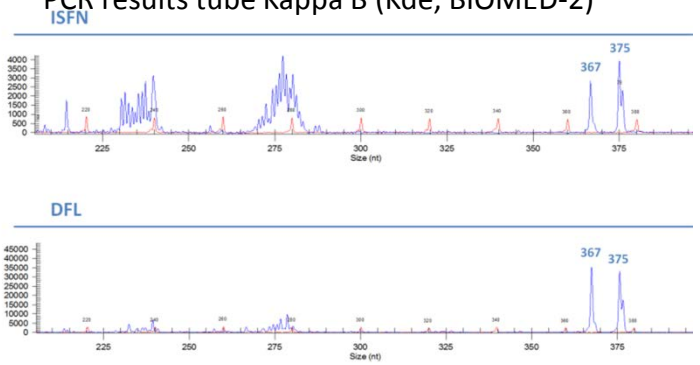
Bcl-2 break apart probe: Positive for t(14;18)

Incidental Peripancreatic LN





PCR results tube Kappa B (Kde, BIOMED-2)



ISFN

DFL

Identical bi-allelic rearrangement in the microdissected duodenal FL and the microdissected in situ follicular neoplasia

Molecular testing revealed relationship between 2 populations

SH2017-0100 **Falko Fend** Institute of Pathology, Tuebingen	Duodenal-type follicular lymphoma with in situ follicular neoplasia-like colonization of abdominal LN germinal centers

Interesting Features

Duodenal (intestinal) FL is regarded as a specific variant of FL with very indolent behavior and very little tendency for dissemination even without therapy.

Duodenal FL is therefore considered similar to in situ follicular neoplasia (ISFN), a precursor lesion of FL with low risk for progression to manifest FL.

Documents the simultaneous appearance of duodenal FL and ISFN, confirming its close relationship.

Genetic events corroborate cell of origin and pathogenetic mechanism and contribute to diagnosis

SH2017-0049 **Zenggang Pan** University of Colorado Denver	FL, grade 1-2 of 3 (with *BCL6* rearrangement)	
SH2017-0193 **Chad Hudson** Janice M. Spence, Paul Rothberg, Hani Katerji, W. Richard Burack University of Rochester	FL, grade 1-2 of 3 [t(14;18) negative]	IGH, IGK GR positive IGHV Mutational Analysis: Highly mutated (82% identity to IGHV1-3*1)
SH2017-0327 **Rohit Gulati** Magdalena Czader Christin Tsao Indiana University	T-cell prolymphocytic leukemia	Rearrangement of TCL1A (14q32) i17p13.1 deletion I deletion of chromosome 11 centromere monosomy 13 I 6q23 deletion Mutation ***TP53***
SH2017-0197 **Chad Hudson** Paul Rothberg, Sapna S. Patel, W. Richard Burack University of Rochester	Primary cutaneous follicle center lymphoma and clonally related diffuse large B-cell lymphoma in the central nervous system	IGH and IGK PCR: clonally related
SH2017-0338 **Andrew Evans** Yi Ding, Todd Laughlin, Paul Rothberg, Carla Casulo, and Richard Burack University of Rochester	EBV+ lymphoproliferative disorder (mucocutaneous ulcer versus diffuse large B-cell lymphoma)	NGS IGH for clonal populations

Molecular testing: precision medicine

- What genes should be included in a panel that may guide therapy?
- What genes should be included in a panel that may inform prognosis?
- What genes should be included in a panel that may predict outcome and treatment response?

What genes should be included in a panel that may guide therapy?

- Obtain specimens for subsequent genetic analysis for investigation of mechanisms of disease resistance and for evaluating candidacy for clinical trials for novel therapies

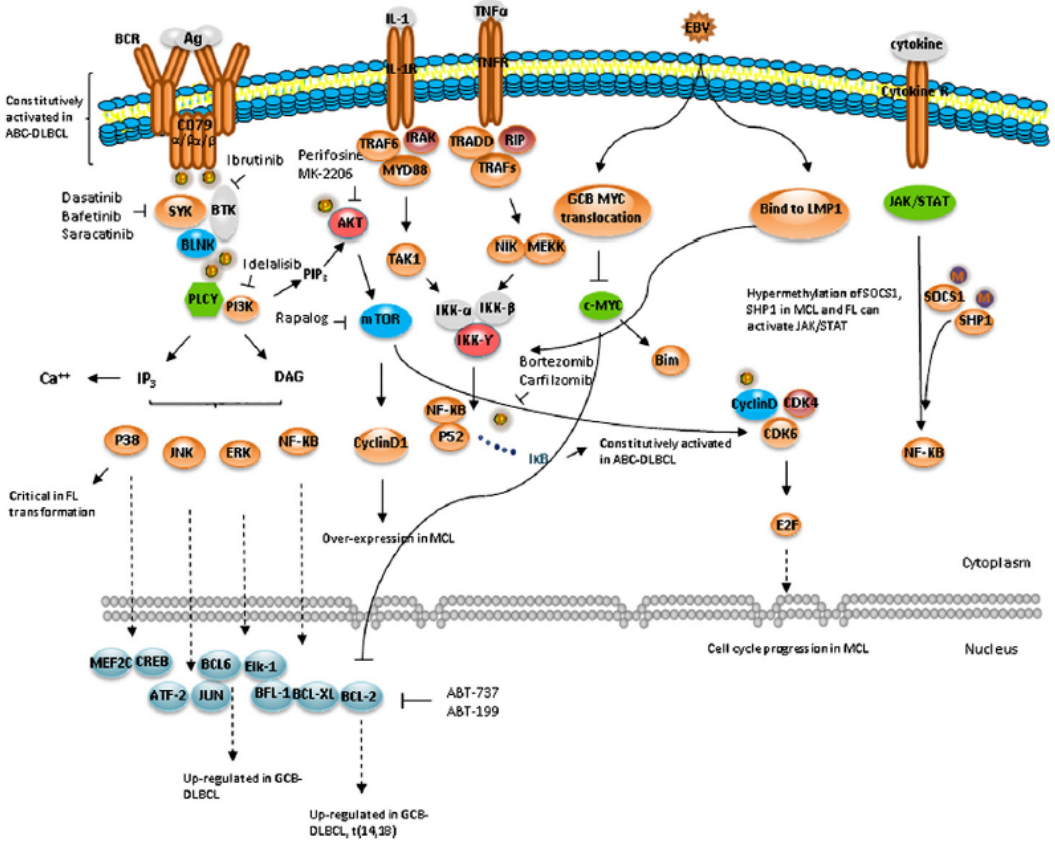
NF-κB pathway

JAK/STAT pathway

BCR signaling pathway

TCR signaling pathway

Epigenetic modifiers



What genes should be included in a panel that may guide therapy?

CLL/SLL

- Currently in clinical and preclinical testing (*SF3B1, TP53, NOTCH1, ATM*)
- Resistance to BCR signaling inhibitors (BTK C481S, BTK T316A, *PLCγ2*)

DLBCL

- FISH for *MYC, BCL6, BCL2* for GCB-subtype
- Mutations in genes associated with ABC, GCB impact prognosis and potentially therapy (*EZH2, CARD11, MYD88, CD79B*)

FCL

- EZH2

MCL, MZBL, Burkitt *???*

What genes should be included in a panel that may guide therapy?

T cell neoplasms

- *JAK1/3* and *STAT3/5B* mutations

- EATL: mutations that affect subclassification (*SETD2*)

  monomorphic EATL are not associated with celiac disease

- *TET2, IDH2* mutations

- ALCL (CD30+, rearrangements of *ALK, DUSP22, VAV, TYK2, JAK2*)

Molecular testing: challenges/pitfalls and novel biologic insights will lead improvements in classification and stratification

What is the clinical significance of clonal evolution?

- Both inter and intra-patient genomic heterogeneity is variable in different lymphoma subtypes.
- Intratumor heterogeneity is high in CLL and contribute to evolution and relapse that may impact selective pressure from tumor microenvironment and chemotherapy or targeted therapies.

What molecular testing is required to assess clonal relationship between two neoplasms?

- Collection of specimens from patients with refractory disease or acquired resistance should be encouraged.
- Immunoglobulin heavy chain or TCR by PCR or NGS
- Tumor-specific mutations or chromosomal alterations

Disease progression and transformation is a heterogeneous biologic process involving different molecular mechanism

- Transdifferentiation
- Clonal evolution
- Clonal divergence
- Lineage plasticity

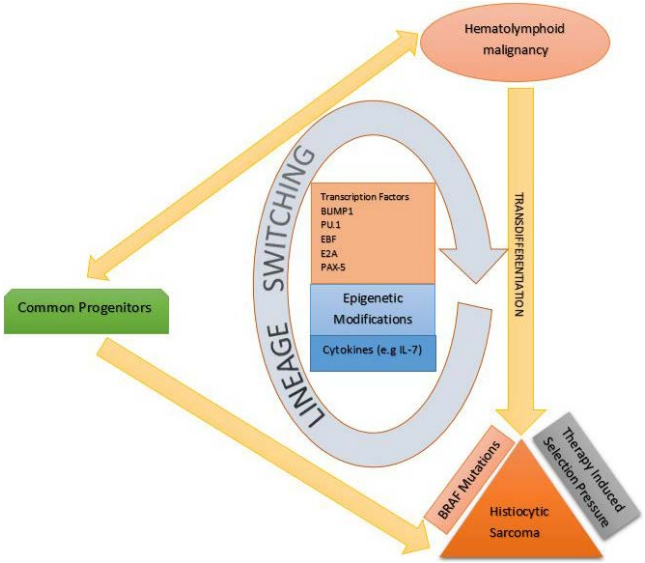
Spontaneous

Post-therapy

CAR-T therapy

Antibody drug congugates

Small molecule inhibitors



Collombet S *et al*. Logical *PNAS* (2017).

Unexpected molecular findings?

- Importance of clinical correlation for underlying malignancy
- Acknowledge the presence of low level genetic alterations in normal populations
- May be associated with subclinical disease progression
- Be prepared to deal with the information

Bon voyage!!