
PATIENT CENTERED CARE
Yuri Fedoriw, MD
Cancer Pathology: How Diagnosis Drives Treatment
May 10
Sound Check
11:55
Start Time
12:00
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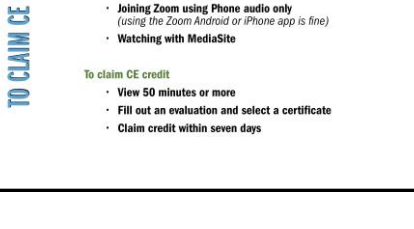
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OUR PRESENTER

Yuri Fedoriw, MD

Yuri Fedoriw, MD is a Distinguished Professor and Vice Chair for Clinical Research and Academic Affairs Co-Director, UNC Project-Malawi Cancer Program.

Since 2011, he has been involved in the UNC Project-Malawi Cancer Program, developing and supporting diagnostic services in support of the Kamuzu Central Hospital Lymphoma Study, AIDS Malignancy Consortium and NIH-funded clinical trials. He now serves as the co- Director of the UNC Project-Malawi Cancer Program, the co-PI of the UNC-Malawi-South Africa Cancer Consortium (U54CA254564) and direct the translational lymphoma studies of samples submitted to UNC through this ongoing work. We have established weekly diagnostic telepathology conferences between Malawian pathologists and clinical teams to improve diagnostic accuracy and build regional capacity for cancer care. We support training in global cancer research through the recently awarded Malawi Cancer Outcomes Research Program (D43CA260641). Fedoriw, MPU that aims to develop global cancer research leaders in Malawi and UNC.

Dr. Fedoriw's research interests focus on the immunologic and genetic mechanisms of lymphomagenesis, particularly in the setting of HIV infection. While hematologic malignancies and lymphoproliferative disorders (including Multicentric Castleman Disease) in sub-Saharan Africa arise under intrinsic and extrinsic pressures very different from those in the United States, comprehensive analyses of these diseases have not been performed. Our laboratory group uses advanced sequencing, immunophenotypic and cellular analysis to address gaps in our understanding of lymphomagenesis and tumor microenvironment in the context of HIV-associated immune dysregulation. Deciphering these tumor-host interactions is critical to better tailor treatment and improve outcomes, particularly in the era of cancer immunotherapy.

Dr. Fedoriw's clinical efforts revolve around the diagnosis and classification of benign and malignant hematolymphoid disorders. He served as the Director of Hematopathology at UNC from 2012-2019, and previously as the Director of the Hematopathology Fellowship Program. He has served on the NCI Lymphoma Clinical Trials Planning Group and the Hematology and Clinical Microscopy Committee for the College of American Pathologists. He is a member of the United States and Canadian Academy of Pathology Education Committee.

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OUR PRESENTER

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OUR PRESENTER

5. He has been a proud member of the UNC Cancer Community and LCCC since 2008

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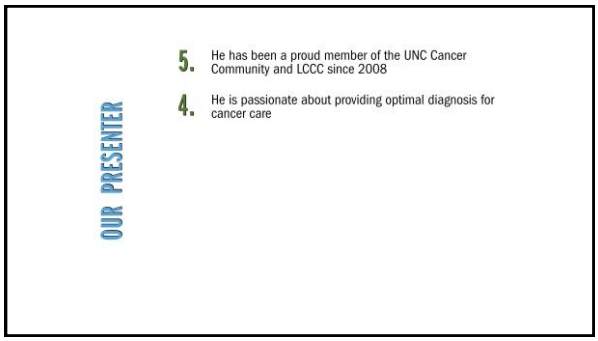
OUR PRESENTER
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4. He is passionate about providing optimal diagnosis for cancer care

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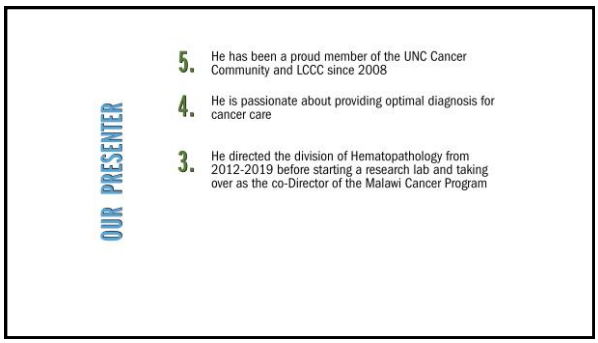
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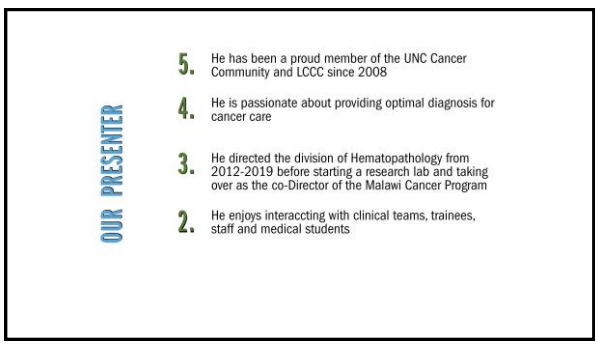
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OUR PRESENTER

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3. He directed the division of Hematopathology from 2012-2019 before starting a research lab and taking over as the co-Director of the Malawi Cancer Program
2. He enjoys interaccting with clinical teams, trainees, staff and medical students
1. Married to a UNC Family Medicine physician which adds an important primary care perspective to cancer diagnosis

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DISCLOSURES

This activity has been planned and implemented under the sole supervision of the Course Director, William A. Wood, MD, MPH, in association with the UNC Office of Continuing Professional Development (CPD). The course director and CPD staff have no relevant financial relationships with ineligible companies as defined by the ACCME.

The University of North Carolina at Chapel Hill is accredited with distinction as a provider of nursing continuing professional development by the American Nurses Credentialing Center's Commission on Accreditation.

A potential conflict of interest occurs when an individual has an opportunity to affect educational content about health-care products or services of a commercial interest with which they have a financial relationship. The speakers and planners of this learning activity have not disclosed any relevant financial relationships with any commercial interests pertaining to this activity.

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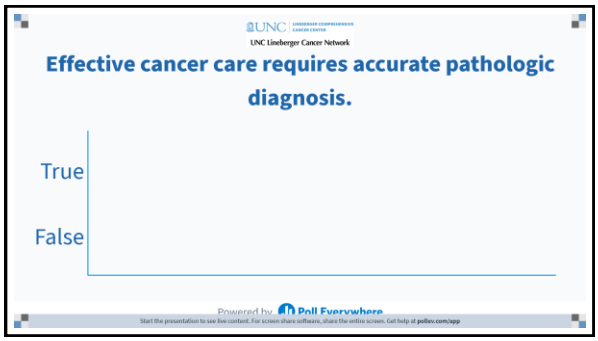

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Cancer Pathology

Yuri Fedoriw, MD
LabCorp Distinguished Professor of Pathology & Laboratory Medicine
Lineberger Comprehensive Cancer Center

UNC SCHOOL OF MEDICINE

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Objectives

1. Describe the evolution of testing methods for cancer diagnosis.
2. Recognize how classification systems are developed to uniformly diagnose tumors.
3. Select appropriate tissue sampling method for cancer diagnosis.
4. Describe the development and application of CAP synoptic reporting for cancer diagnoses

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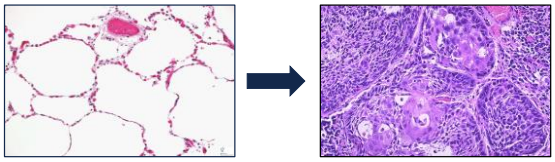
Background



Normal Lung Lung Cancer

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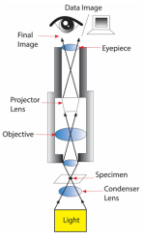
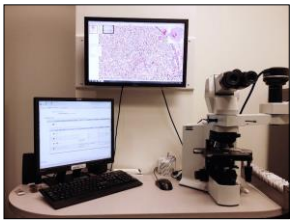
Microscopy





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Question 1

When a patient has a breast lumpectomy, when are the first slides ready to review by a pathologist?

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UNC Lineberger Cancer Network
When a patient has a breast lumpectomy, when are the first slides ready to review by a pathologist?
After 5-10 hours
1-2 days
1 week
> 2 weeks
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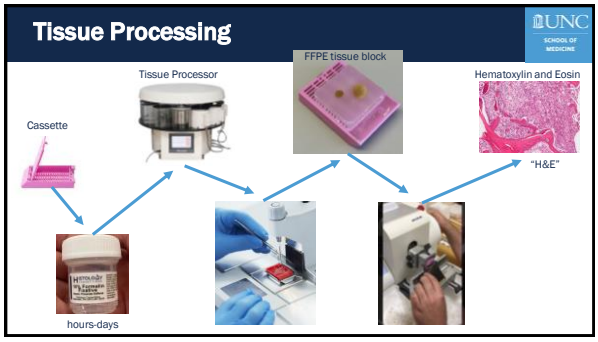
Tissue Processing
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Tissue Processor
FFPE tissue block
Hematoxylin and Eosin
Cassette
"H&E"
hours-days

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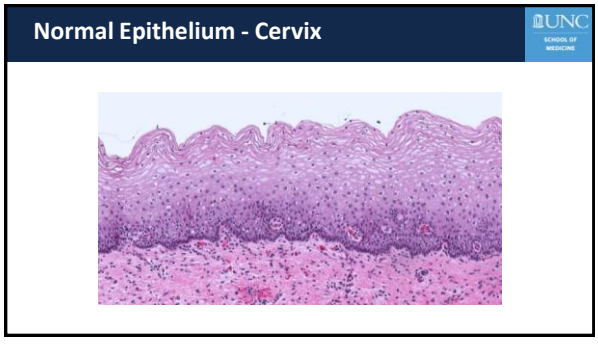
Normal Epithelium - Cervix
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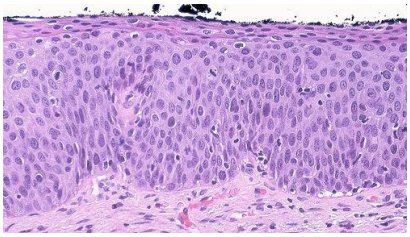
Dysplastic Epithelium - Cervix



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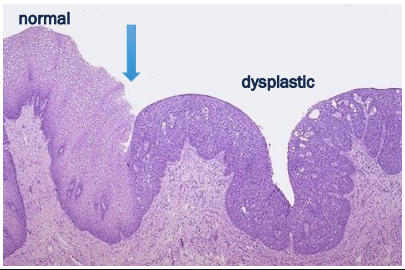
Dysplasia – Cervical Dysplasia (HPV)



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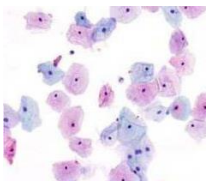
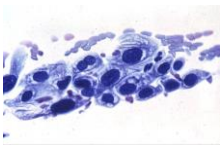
Cytopathology



Benign Squamous Epithelial Cells



Dysplastic Epithelial Cells

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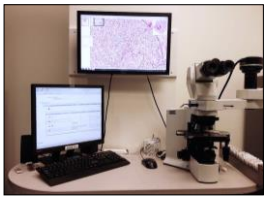
Microscopy



Chapel Hill

Lilongwe, Malawi

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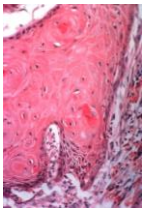
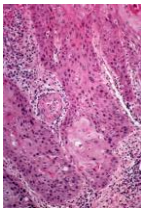
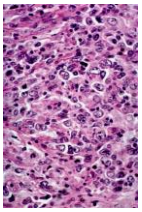
"Grade" – Squamous Cell Carcinoma



Well-differentiated



Moderately-differentiated



Poorly-differentiated

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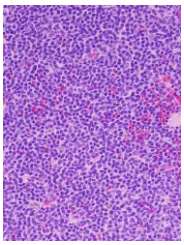
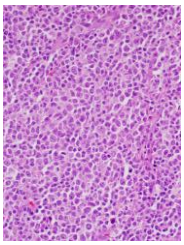
Grade – Follicular Lymphoma



Low-grade



High-grade

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Question 2

Colon cancers are common. A series of studies identifies a gene mutation associated with particularly poor outcomes. In this example, the gene represents:

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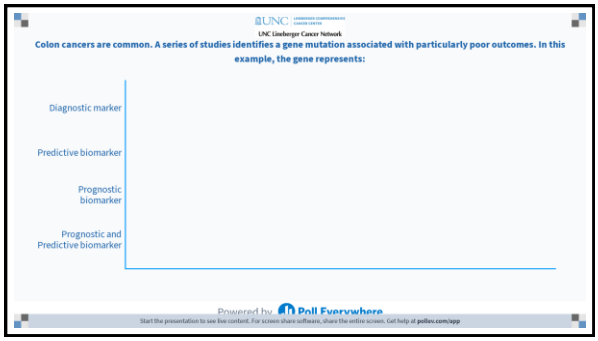

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Evolution of Diagnostic Testing

- Not all cancers that *looked* the same *acted* similarly
- Cellular and molecular biology research → mechanisms of disease and features that are:
  - Diagnostic
  - Prognostic
  - Predictive
- Technology and understanding of biology → clinical care

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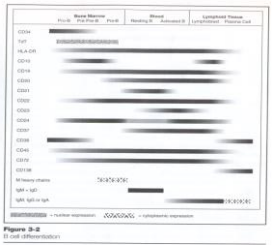
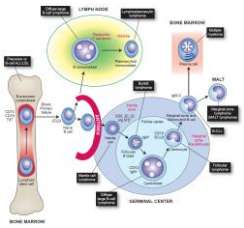
B-cell Lymphomas - from maturation and classification





Shaffer AL 3rd, Young RM, Staudt LM. Pathogenesis of human B cell lymphomas. *Annu Rev Immunol*. 2012;30:565-610.

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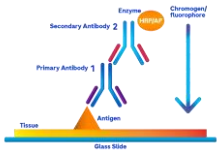
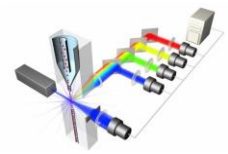
Immunophenotyping

Immunohistochemistry



Flow Cytometry



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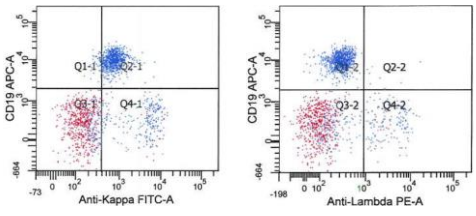
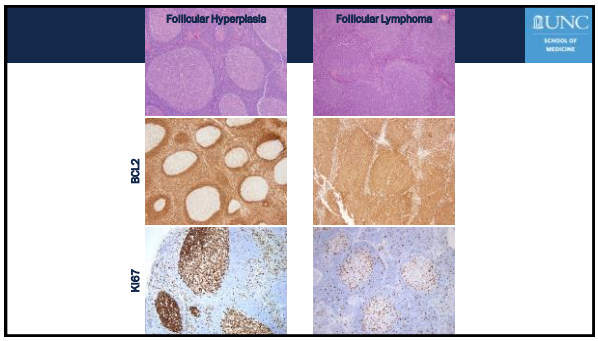
Example of Flow Cytometry



36



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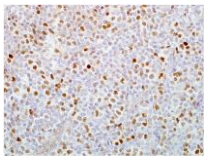
… the staining is rarely "binary"

- Some stains work better than others
  - Biologic
  - Technical
- Reporting for many clinically actionable/important stains is subjective



cMYC expression:
- >40% is considered +
- What would YOU call this?

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Other testing methods

- Karyotype ("routine cytogenetics")
- Fluorescence *in situ* hybridization (FISH)
- Sequencing

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Karyotype

- Culture cells → arrest in metaphase → stain
- Advantages:
  - Unbiased look at the entire genome
  - Identify large aberrations
- Disadvantages:
  - Poor resolution

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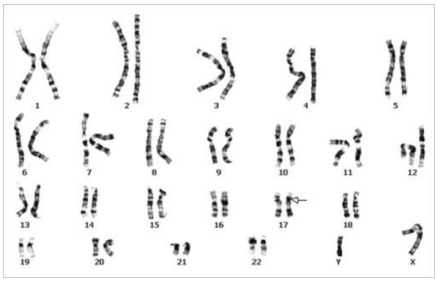

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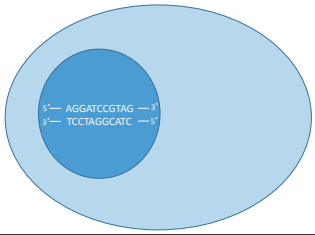
Fluorescence *in situ* hybridization

- Fluorescent DNA probes are hybridized to specific sequences of interest



43

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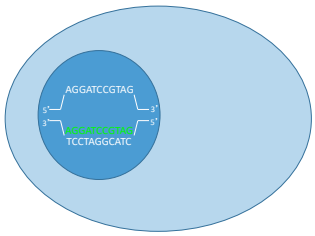

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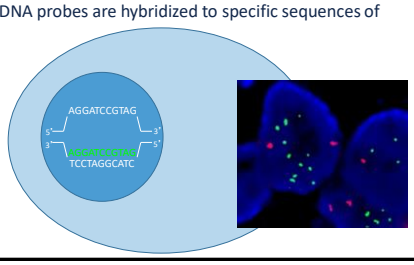
Fluorescence *in situ* hybridization

- Fluorescent DNA probes are hybridized to specific sequences of interest



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Fluorescence *in situ* hybridization

- Advantages:
  - Increased resolution compared to karyotype
- Disadvantages:
  - User defines the target

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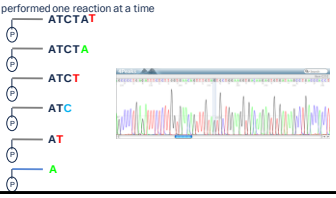
DNA Sequencing

Classical sequencing methodology – Sanger dideoxy sequencing

- Permanent chain terminator method
- Template DNA, sequencing primer, DNA polymerase, deoxynucleotides (dA,dG,dT,dC) and labeled dideoxynucleotides (ddA, ddG, ddT, ddC) are all combined in a single reaction
- Sequencing is performed one reaction at a time



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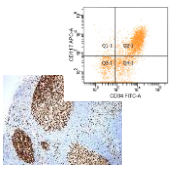
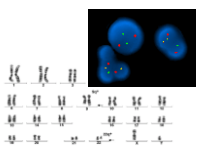
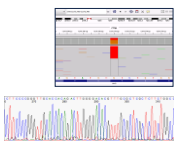
Evolution of testing



Immunophenotyping



Cytogenetics/FISH



Molecular Studies

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Why is Uniform Classification Important?

- Patient Care
  - Diagnosis
  - Prognostic – outcome
  - Predictive – predict response to therapies
- Clinical Trials
- Public Health and Policy (accurate cancer registries)

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Classification Systems

International Agency for Research on Cancer

World Health Organization

https://tumourclassification.iarc.who.int/welcome/

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Classification of Myeloid Cancers

Myeloproliferative neoplasms
Chronic myeloid leukemia, *BCR-ABL1+*
Chronic neutrophilic leukemia
Polycythemia vera
Primary myelofibrosis
Essential thrombocythemia
Chronic eosinophilic leukemia
MPN, unclassifiable

Mastocytosis
Cutaneous mastocytosis
Systemic mastocytosis

Myeloid/lymphoid neoplasms with eosinophilia and abnormalities of *PDGFRA*, *PDGFRB*, *FGFR1*, or with *PCM1-JAK2*
Myeloid/lymphoid neoplasms with *PDGFRA* rearrangement
Myeloid/lymphoid neoplasms with *PDGFRB* rearrangement
Myeloid/lymphoid neoplasms with *FGFR1* rearrangement
Myeloid/lymphoid neoplasms with *PCM1-JAK2*

MDS/MPN neoplasms
CMML
Atypical CML
JMML
MDS/MPN with ring sideroblasts and thrombocytosis
MDS/MPN, unclassifiable

Myelodysplastic syndrome
MDS with single lineage dysplasia
MDS with ring sideroblasts
MDS with multilineage dysplasia
MDS with excess blasts
MDS with isolated del(5q)
MDS, unclassifiable
Refractory cytopenia of childhood

Acute myeloid leukemia
AML with t(8;21)
AML with inv(16)
AML with *PML-RARA*
AML with t(9;11)
AML with t(6;9)
AML with inv(3)
AML with t(1;22)
AML with *BCR-ABL1*
AML with mutated *NPM1*
AML with biallelic mutations of *CEBPA*
AML with mutated *RUNX1*
AML with myelodysplasia related changes
Therapy-related AML
AML, NOS

Other myeloid malignancies
Myeloid neoplasms with germline predisposition
Myeloid proliferations related to Down syndrome

Molecular/cytogenetic feature specifically part of diagnostic criteria

Molecular/cytogenetic feature not specifically part of the diagnostic criteria

Arber DA et al. *Blood* 2016; 127:2391-2405

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Review of Referral Cases

- Inconsistencies in diagnosis
  - Some could be true "errors"
  - Many reflect access to improved technologies, updated clinical history and imaging, new laboratory findings from presentation to referral, etc.
- Requirement for review of diagnostic material before treatment

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Discordance with Non-Hodgkin Lymphoma Diagnoses

- National Comprehensive Cancer Network NHL database
- 731 patients with the 5 most common lymphoma types
- 43 (6%) were discordant from primary to NCCN center review
- 35 of 43 may have had a change in treatment!
- Depending on tumor type, discordance can be >25%

Comparison of Referring and Final Pathology for Patients With Non-Hodgkin's Lymphoma in the National Comprehensive Cancer Network
Ann S. LaCasce, Michelle E. Kho, Jonathan W. Friedberg, Joyce C. Niland, Gregory A. Abel, Maria Alma Rodriguez, Myron S. Czuczman, Michael M. Millenson, Andrew D. Zelenetz, and Jane C. Weeks
Journal of Clinical Oncology 2008 26:31, 5107-5112

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Question 3

A study of human pancreatic tumors implanted into mice identifies a new prognostic biomarker by immunohistochemistry. The findings are reported in a high-impact journal and antibody for testing is available from the research lab. Can you use this test for clinical decision making?

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College of American Pathologists

- Council on Accreditation
- Council on Education
- Council on Government and Professional Affairs
- Council on Membership and Professional Development
- **Council on Scientific Affairs**
  - Anatomic Pathology, Chemistry, Hematology, Informatics, Laboratory General, Molecular Pathology
- Committees of the Board of Governors

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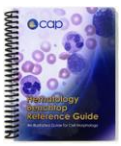
College of American Pathologists

- Primary responsibilities:
  - Survey development and review (100's/year)
  - Revisions of inspection checklist
  - Glossary upkeep



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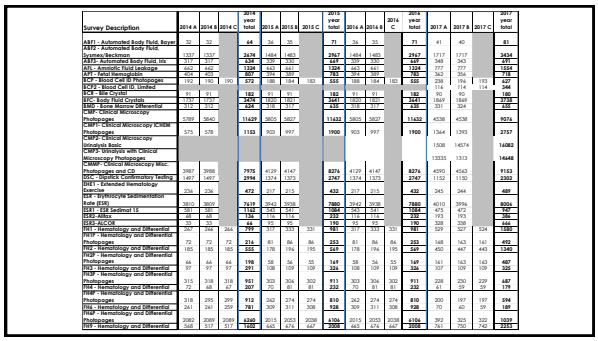

Survey Description	2014 A	2014 B	2014 C	2014 year total	2015 A	2015 B	2015 C	2015 year total	2016 A	2016 B	2016 C	2016 year total	2017 A	2017 B	2017 C	2017 year total
ABF - Automated Body Fluid, Bayer	32	32		**64**	34	35		**71**	36	35		**71**	41	40		**81**
ABW - Automated Body Fluid, Beckman Coulter	1357	1329		**2678**	1484	1483		**2967**	1484	1483		**2967**	1717	1717		**3434**
ABX - Automated Body Fluid, Iris	317	317		**634**	330	330		**647**	330	330		**659**	346	343		**689**
AFL - Amniotic Fluid Leakage	663	662		**1324**	663	661		**1324**	663	661		**1324**	777	777		**1554**
AFF - Fetal Hemoglobin	804	803		**807**	394	389		**783**	394	389		**783**	362	356		**718**
BCF - Blood Cell ID Photogogen	192	190	190	**572**	188	184	183	**555**	188	184	183	**555**	238	194	193	**627**
BCFZ - Blood Cell ID, Unified													114	114	114	**344**
BCR - Bile Crystal	91	91		**182**	91	91		**182**	91	91		**182**	90	90		**180**
BFC - Body Fluid Crystals	1757	1734		**3474**	1800	1801		**3441**	1800	1801		**3441**	1669	1669		**3338**
BMD - Bone Marrow Differential	312	312		**624**	318	317		**635**	318	317		**635**	331	324		**655**
CMP - CliniCal Microscopy Photogogen	3789	3840		**11629**	3855	3807		**11532**	3855	3807		**11532**	4538	4538		**9076**
CMPF - CliniCal Microscopy IC_HEM Photogogen	575	576		**1152**	485	997		**1900**	903	997		**1900**	1364	1395		**2757**
CMPZ - CliniCal Microscopy Urinalysis Basic													1008	14674		**14682**
CMPZ - Urinalysis with CliniCal Microscopy Photogogen													13335	13313		**14648**
CMWP - CliniCal Microscopy Misc. Photogogen and CO	3987	3988		**7975**	4128	4147		**8274**	4129	4147		**8274**	4590	4543		**9133**
EDC - Diginstick Confirmatory Testing	1467	1467		**2934**	1374	1373		**2747**	1374	1373		**2747**	1152	1150		**2302**
ERET - Extended Hematology Exercise	236	236		**472**	217	215		**432**	217	215		**432**	245	244		**489**
ESR - Erythrocyte Sedimentation Rate (ESR)	3810	3809		**7619**	3940	3938		**7880**	3940	3938		**7880**	4010	3996		**8006**
ESR1 - ESR Sedimat 15	581	581		**1162**	541	541		**1082**	541	541		**1082**	475	472		**947**
ESRM - ESR Manual	88	88		**176**	116	116		**232**	116	116		**232**	193	193		**386**
ELSD - ALCOR	48	48		**96**	48	48		**96**	48	48		**96**	48	48		**96**
H91 - Hematology and Differential	357	356	344	**709**	357	339	331	**1027**	357	339	331	**1027**	529	527	524	**1580**
H91F - Hematology and Differential Photogogen	72	72	72	**216**	81	86	86	**253**	81	86	86	**253**	148	163	161	**472**
H92 - Hematology and Differential	185	185	185	**555**	178	196	195	**569**	178	196	196	**569**	450	447	443	**1340**
H92F - Hematology and Differential Photogogen	44	44	44	**196**	38	56	55	**149**	38	56	52	**149**	141	163	143	**487**
H93 - Hematology and Differential	97	97	97	**291**	108	109	109	**326**	108	109	109	**326**	107	109	109	**325**
H93F - Hematology and Differential Photogogen	315	318	318	**951**	303	304	302	**911**	303	304	303	**911**	228	230	229	**687**
H94 - Hematology and Differential	72	68	67	**207**	70	81	81	**232**	70	81	81	**232**	61	59	59	**179**
H94F - Hematology and Differential Photogogen	318	295	299	**912**	342	274	274	**810**	342	274	274	**810**	200	197	197	**594**
H95 - Hematology and Differential	241	241	239	**781**	309	311	308	**928**	309	311	308	**928**	70	69	59	**198**
H95F - Hematology and Differential Photogogen	3082	2089	3089	**6260**	3015	2053	3038	**4106**	3015	2053	3038	**4106**	392	322	322	**1039**
H99 - Hematology and Differential	548	317	317	**1482**	685	674	647	**2005**	685	674	647	**2005**	761	290	742	**2253**

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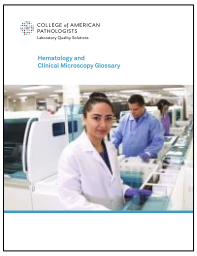
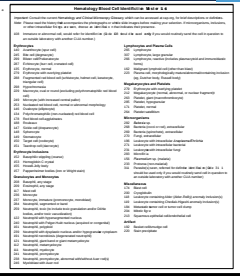
CAP Glossary





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Synoptic Reporting for Cancer Diagnosis

College of American Pathologists (CAP)

- One of the leading pathology organizations
- Oversee laboratory accreditation (… more on this soon!)
- Many studies in the 90's revealed significant variation in cancer reporting → CAP cancer committee reporting checklists

https://www.cap.org/protocols-and-guidelines/cancer-reporting-tools/cancer-protocol-templates

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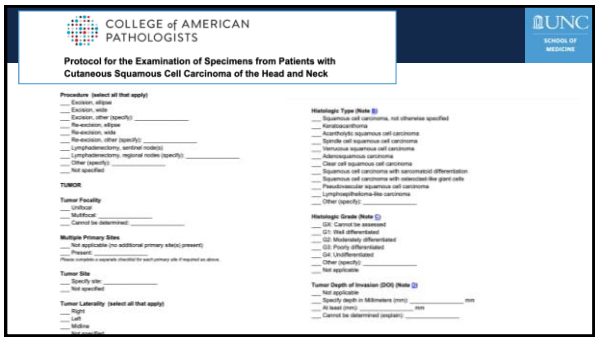
COLLEGE of AMERICAN PATHOLOGISTS

Protocol for the Examination of Specimens from Patients with Cutaneous Squamous Cell Carcinoma of the Head and Neck

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Synoptic Reporting for Cancer Diagnosis

- Checklists improve completeness
- Improved accuracy (to a point)

- For those who read them:
  - Consistent formatting
  - Columned vs. justified
  - Single-line vs. multiple lined

Synoptic Reporting: Evidence-Based Review and Future Directions
Andrew A. Renshaw, Mercy Mena-Allauca, Edwin W. Gould, and S. Joseph Sirintrapun
JCO Clinical Cancer Informatics 2018 :2, 1-9

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Tissue Sampling for Diagnosis

- Specimen adequacy is a major challenge in clinical practice
- Limited sampling can lead to missed or delayed diagnosis
- Insufficient tissue for study enrollment or correlative science

- In response to the trend, other diagnostic methods (liquid biopsies, etc) are being developed

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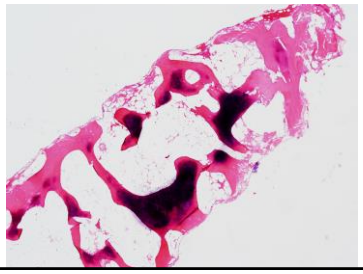
Bone marrow biopsy

Hypocellular bone marrow?
- Aplastic anemia
- Drug/toxin effect
- Hypocellular MDS
- GVHD



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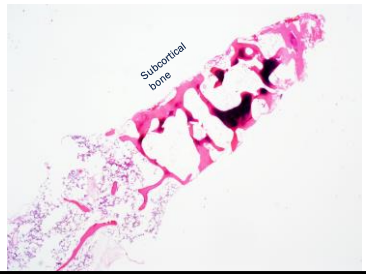
Bone marrow biopsy

... or maybe not!?!



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Fine Needle Aspirate vs Tissue Biopsy

- Advantages of FNA
  - Simple procedure
  - Low morbidity
  - Efficiently guides patient triage
- Disadvantages of FNA
  - Sampling
  - No histologic architecture
  - Frequently needs follow-up excisional biopsy

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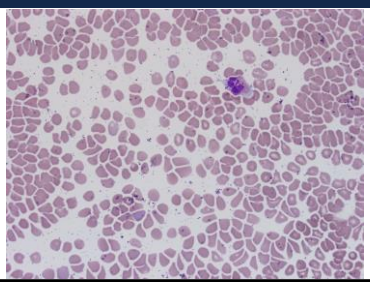
FNA – 5cm axillary lymph node



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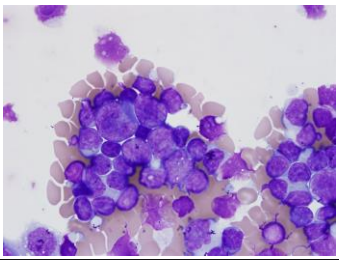
Follow-up FNA: Lymphoma



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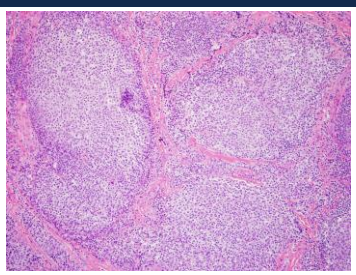
Excisional biopsy – Follicular Lymphoma



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Conclusions

- Effective cancer care requires accurate pathologic diagnosis
- Testing methods have evolved that reflect our understanding of cancer biology and allow for improved reporting of prognostic and predictive biomarkers
- While new technologies are being developed to do 'more with less' adequate tissue biopsies are necessary (perhaps more than ever before)
- Synoptic reporting allows for discrete data elements to be provided for consistency and data collection.

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UNC SCHOOL OF MEDICINE

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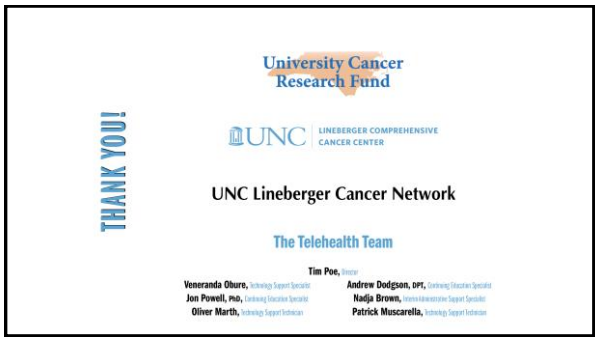
THANK YOU!
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UNC Lineberger Cancer Network
The Telehealth Team
Tim Poe, Director
Veneranda Obure, Technology Support Specialist
Jon Powell, PhD, Continuing Education Specialist
Oliver Marth, Technology Support Technician
Andrew Dodgson, DPT, Continuing Education Specialist
Nadja Brown, Videoconferencing Support Specialist
Patrick Muscarella, Technology Support Technician

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UPCOMING LIVE WEBINARS
ADVANCED PRACTICE PROVIDER
May 17
4:00 PM
Oncologic Emergencies: Neutropenic Fever, Cord Compression, Tumor Lysis Syndrome
Laura Blanchard, MPAP, PA-C
RESEARCH TO PRACTICE
May 24
12:00 PM
Radiation Oncology Management of Lung Cancer in NC: Update on Small-Cell Lung Cancer
Ashley Weiner, MD, PhD
PATIENT CENTERED CARE
June 14
12:00 PM
Psychotherapy for Cancer-Related Distress
Melissa Holt, DNP, PMHNP-BC, MSW
Lisa Stewart, Psy.D.
Complete details on upcoming Live Webinars:
learn.uncln.org/live-webinars

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SELF-PACED, ONLINE COURSES
ADVANCED PRACTICE PROVIDER
What Is Cancer Rehabilitation and How Can it Help My Patients
Sasha Knowlton, MD
RESEARCH TO PRACTICE
Clinical Updates in Breast Oncology
Emily Ray, MD, MPH
PATIENT CENTERED CARE
Integrating the Caregiver as a Member of the Multidisciplinary Care Team
Erin E. Kent, PhD, MSc
Loretta Muss, RN, BA
Complete details on upcoming Live Webinars:
learn.uncln.org/live-webinars

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