Office Tips

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• Physician fatigue
• New Diagnostic tests:
  - Clonoseq for atypical lymphoid infiltrates
  - Fungitell for chronic ulcers
  - 31 Gene Expression Profile for melanoma prognosis
• Biotin
• Raynaud phenomenon
• Lyme disease
• HPV vaccine to prevent SCC
• Zoster vaccine
Doctor fails: early warning signs of physician fatigue?
BMJ. 2017 Dec 12;359:j5503
Linos E, Admassu N, Sabry-Elnaggar H, Li PM, Choo E.

“Doctor fatigue is no laughing matter. Fatigue due to sleep deprivation and long work hours is a well recognised problem in medicine. Fatigue among doctors poses risks to patients, as medical mistakes are more common when doctors are tired. In addition, doctors who work longer hours have higher rates of burnout, depression, and car crashes. In response to these concerns, both the United States Accreditation Council on General Medical Education and the European Working Time Directive have imposed restrictions on the number of work hours for doctors in training.”
Tip #1: DRINK COFFEE. You can always sleep when you die!
My diagnosis:
Lichen Spinulosis

Grand Rounds:
Could it be
Follicular mycosis fungoides?
NEW YORK (GenomeWeb) – A team from Dana-Farber Cancer Institute, Brigham and Women's Cancer Center, Harvard Medical School, and Adaptive Biotechnologies has identified characteristic T cell receptor beta gene patterns coinciding with particularly aggressive cases of mycosis fungoides (MF), a form of cutaneous T cell lymphoma (CTCL) affecting CD4+ T cells with alpha and beta T cell receptor subunits.

The researchers used high-throughput T cell receptor beta gene (TCRB) sequencing to assess skin biopsy samples from 208 individuals with CTCL, including 177 MF cases. During a 15-year observational study, they found that increasing tumor clone frequency in the CTCL skin lesion biopsies typically coincided with poorer progression-free survival and overall survival times, particularly for individuals with MF.
High-throughput sequencing of the T cell receptor β gene identifies aggressive early-stage mycosis fungoides.


Tumor clone frequency >25% in lesional skin predicts progressive disease in CTCL
clonoSEQ®

NOW FDA-CLEARED AND COVERED BY MEDICARE

for patients with

MULTIPLE MYELOMA

&

B-CELL ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)
For “atypical lymphoid infiltrate”
ClonoSEQ assay
Adaptive Biotechnologies

https://www.adaptivebiotech.com/clonoseq/clonoseq-assay

Tip#2: Clonoseq for atypical lymphoid infiltrates
Application of the 1,3-β-D-Glucan (Fungitell*) Assay in the Diagnosis of Invasive Fungal Infections.
Tran T, Beal SG.

- In cell wall of Candida spp, Aspergillus spp, Fusarium spp, Pneumocystis jiroveci, Coccidioides immitus, Histoplasma capsulatum, Blastomyces dermatidis

- sensitivity 78%, specificity 98.4%

*Associates of Cape Cod, East Falmouth, MA
Fungitell® β-D-Glucan Assay

Test Code: 1700

Clinical and Procedure

Clinical Utility

The Fungitell β-D Glucan assay is indicated for the presumptive diagnosis of invasive fungal disease through detection of elevated levels of (1,3)-β-D-glucan in serum. Normal human serum contains low levels of (1,3)-β-D-glucan, typically 10 to 40 pg/mL, presumably from commensal yeasts present in the alimentary canal and gastrointestinal tract. However, (1,3)-β-D-glucan is sloughed from the cell walls during the life cycle of most pathogenic fungi. Thus, monitoring serum for evidence of elevated and rising levels of (1,3)-β-D-glucan provides a convenient surrogate marker for invasive fungal disease.
31 gene expression test was developed to assess risk of recurrence independent from traditional clinico-pathologic factors using tumor biology

31 GENE EXPRESSION
- Quantifies expression of 31 genes from primary tumor using RT-PCR
- Applies a validated algorithm
- Accurately classifies patients as low or high risk

Class 1:
- Low risk of melanoma recurrence within 5 years
  - 1A: Lowest risk
  - 1B: Low risk

Class 2:
- High risk of melanoma recurrence within 5 years
  - 2A: Increased risk
  - 2B: Highest risk


### Stage I
- **Melanoma Specific Survival (%):** 99.6%
- **Risk Category:** Low Risk
- **NCCN Stage:** I

### Stage II
- **Melanoma Specific Survival (%):** 89.5%
- **Risk Category:** Low Risk
- **NCCN Stage:** IIA/IIB

### Stage III
- **Melanoma Specific Survival (%):** 84.7%
- **Risk Category:** Low Risk
- **NCCN Stage:** IIB/IIC

### Stage IIB
- **Melanoma Specific Survival (%):** 61.2%
- **Risk Category:** Low Risk
- **NCCN Stage:** IIIC+

### Stage III
- **Melanoma Specific Survival (%):** 94.8%
- **Risk Category:** Low Risk
- **NCCN Stage:** III

Class 1A
- **Melanoma Specific Survival (%):** 98%
- **Risk Category:** Low Risk
- **NCCN Stage:** IA

Class 2B
- **Melanoma Specific Survival (%):** 77%
- **Risk Category:** Low Risk
- **NCCN Stage:** IIA
31 gene expression test test has shown consistent results across 3 archival and 3 prospective studies totaling over 1,300 unique patients.
31 gene expression test subclass can predict SLNB positivity risk for patients with T1-T2 tumors and inform SLNB guidance

**SLN+ probability in T1-T2 patients:**
- Is below the 5% threshold established by guidelines in those ≥55 years old with a Class 1A result
- Is above the 10% threshold established by guidelines in all age groups with a Class 2B result

**NCCN Recommendations for SLNB (v2.2018):**
- Discuss and Offer
  - <55: 7.6%
  - 55-64: 4.9%
  - ≥65: 1.6%
- Discuss and Consider
  - <55: 19.6%
  - 55-64: 7.7%
  - ≥65: 6.9%
- Do not Recommend
  - <55: 24.0%
  - 55-64: 30.8%
  - ≥65: 11.9%

**31 gene expression test subclass can predict SLNB positivity risk for patients with T1-T2 tumors and inform SLNB guidance:**

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**Thresholds based on NCCN Guidelines (v2.2018):**
- n=1,065

**Tip#4**
Brittle nails: response to daily biotin supplementation.

- 25 percent increase in nail plate thickness
- 63 % showed clinical improvement
Characterization of the scope and magnitude of biotin interference in susceptible Roche Elecsys competitive and sandwich immunoassays.
Trambas C, et al.

Discordant analytical results caused by biotin interference on diagnostic immunoassays in a pediatric hospital.
Ali M, Rajapakshe D, Cao L, Devaraj S.
Biotin treatment mimicking Graves’ disease.
Kummer S, Hermsen D, Distelmaier F.

Factitious Graves’ disease due to biotin immunoassay interference—A case and review of the literature.
Elston MS, et al.

Misdiagnosis of Graves’ hyperthyroidism due to therapeutic biotin intervention.
De Roeck Y, et al.

US Food and Drug Administration
Rethinking biotin therapy for hair, nail, and skin disorders.
Lipner SR.

Tip#5
Severe refractory fingertip ulcerations in a patient with scleroderma: successful treatment with sildenafil.

Use of tadalafil in a patient with a secondary Raynaud's phenomenon not responding to sildenafil.

A systematic review and meta-analysis of the effects of topical nitrates in the treatment of primary and secondary Raynaud's phenomenon.

Statins: Potentially useful in therapy of systemic sclerosis-related Raynaud’s Phenomenon and digital ulcers.
Abou-Raya A et al.

- **Atorvastatin 40/d vs placebo x 4 mos**
- new ulcers: 1.6 vs 2.5
- **↓** RP, **↓** pain and severity of ulcers,
  **↓** endothelial damage markers
Botox therapy for ischemic digits.
Neumeister MW et al.

- 100 unit botulinum toxin vial diluted in 2cc preservative-free saline
- 50-100 U of toxin injected into palm around neuromuscular bundles at MCP
- pain relief was immediate
- ulcers healed within 2 months
- Doppler showed increased blood flow within 30 minutes
- pain relief persisted in 12/19 at 13-59 months
Management of vasospastic disorders with botulinum toxin A.
Van Beek AL et al. 

- 11 patients, painful Raynaud’s, digital ulcerations.
- Failed vasodilators, anti-platelet agents, and IV prostacyclin.
Botox 100 U at 8-10 sites, perivascular digital and palmar.

- Temporary hand weakness in 3 patients.
- All patients improved:
  - Less frequent and less severe vasospasm and cyanosis within 48 hours.
  
    PreRx scores: 9-10

PostRx: 0-2

Van Beek AL et al.  
Clinical predictors of Lyme disease among children with a peripheral facial palsy at an emergency department in a Lyme disease-endemic area.
Nigrovic LE, et al

• Facial palsy was attributed to Lyme disease in 34% of children with peripheral facial palsy in a Lyme endemic area.
Complications of Untreated Lyme Disease

• Cardiac sx 5-8%
• Neurologic sx 15-20%
• Arthritis 30-60%

Tibbles CD, Edlow JA.
JAMA 2007;297:2617-27
Cultivation of Borrelia burgdorferi from human tick bite sites: a guide to the risk of infection.
Berger BW, Johnson RC, Kodner C, Coleman L.

- B. Burgdorferi cultivated from only 2/48 bites, both present >24h.
- Risk of infection low if tick present <24h.

Tip#7A
Prophylaxis with single-dose doxycycline for the prevention of Lyme disease after an *Ixodes scapularis* tick bite.


- Single 200 mg doxycycline within 72h of tick removal can prevent Lyme disease.
• Erythema migrans typically precedes the development of antibodies
• some patients with early neurologic manifestations will need a repeat test in 1 to 2 weeks for a result to become positive
• Virtually all patients with Lyme arthritis (a late manifestation of Lyme disease) will have a positive IgG
• 10% of men and 15% of women were either exhausted or very tired either every day or most days in the previous 3 months; 17% of the men and 21% of the women often had pain in the previous 3 months
• vast majority of positive results will be falsely positive, esp in nonendemic area
• 42% incorrectly interpreted a positive IgM result alone as an overall positive result; longstanding disease→+IgG
• American Academy of Pediatrics endorsed short-term (<21 days) use of doxycycline for Lyme disease in children younger than 8 years based on the low risk of dental staining in reports of treatment of a relatively small number of young children with RMSF
• Appropriate for single-dose prophylaxis for a high-risk tick bite or treatment of either Lyme meningitis
• amoxicillin and cefuroxime axetil are as effective as doxycycline to treat erythema migrans

Combined Systemic and Intratumoral Administration of Human Papillomavirus Vaccine to Treat Multiple Cutaneous Basaloid Squamous Cell Carcinomas.


JAMA Dermatol. 2018 Jul 3. [Epub ahead of print]

- 90 yo ♀ numerous scc’s RLE
- 2 doses of 9-valent vaccine 6w. apart
- at w. 9, 3 tumors rx’d IL with 0.5cc
- 3 additional tumors rx’d over next 8mos.
HPV viral load determination during pregnancy as a possible cervical cancer risk.


• 68% of pregnant women have evidence of HPV infection
The near disappearance of genital warts in young women 4 years after commencing a national human papillomavirus (HPV) vaccination programme.

Read TRH, et al.

*Sex Transm Infect.* 2011;87:544-7.
Quadrivalent vaccine proves highly effective in preventing HPV-associated anogenital warts and intra-epithelial neoplasms of the cervix, vagina, and vulva.

Garland S et al.  

- 3 yr follow-up
- Vaccine 100% effective against genital warts, VIN, CIN, cancer
Reduced prevalence of oral human papillomavirus (HPV) 4 years after bivalent HPV vaccination in a randomized clinical trial in Costa Rica.

Herrero R et al.

Human papillomavirus and rising oropharyngeal cancer incidence in the United States.

Chaturvedi AK, et al.

Differences in history of sexual behavior between patients with oropharyngeal squamous cell carcinoma and patients with squamous cell carcinoma at other head and neck sites.


Oropharyngeal SCC assoc. w/ ↑ oral sex partners

- >9 lifetime sex partners (OR 39.2 [CI 8.2-187.3])
- >4 oral-genital sex partners (OR 8.6 [CI, 2.2-33.4])

Coffee consumption and the risk of oral, pharyngeal, and esophageal cancers in Japan: the Miyagi Cohort Study.
Naganuma T, et al.

coffee consumption was associated with a lower risk of oral, pharyngeal, and esophageal cancers
A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults.

Oxman MN et al.


- 38,546 adults ≥ 60  1:1
- **Zoster:** vaccine – 315, placebo – 642
- **PHN:** vaccine – 27, placebo - 80
• Vaccine reduced zoster incidence by 51.3%.

• Reduced post-herpetic neuralgia by 66.5%.


• efficacy: 97.2% (95% CI, 93.7 to 99.0; P<0.001)
• severe ISR & systemic reactions within 7d: 17% vaccine, 3.2% placebo
Efficacy of the Herpes Zoster Subunit Vaccine in Adults 70 Years of Age or Older. 
Cunningham AL, et al

- efficacy against herpes zoster: 91.3% 
  (95% CI, 86.8 to 94.5; P<0.001)
- efficacy against postherpetic neuralgia: 88.8%  
  (95% CI, 68.7 to 97.1; P<0.001)
- ISR & systemic rxn within 7d: (79.0% vs. 29.5%).
Immunogenicity and Safety of the HZ/su Adjuvanted Herpes Zoster Subunit Vaccine in Adults Previously Vaccinated with a Live-Attenuated Herpes Zoster Vaccine.

Grupping K, et al

Long-term immunogenicity and safety of an investigational herpes zoster subunit vaccine in older adults.
Chlibek R, et al.

• 6 yrs p. vaccine → IgE-specific CMI & anti-gE ab ↓ 20-25% from month 36, but > prevaccination values.
• 6 yrs → IgE-specific CMI → 3.8 times prevaccination value & anti-gE antibody concentration → ↑ 7.3 times