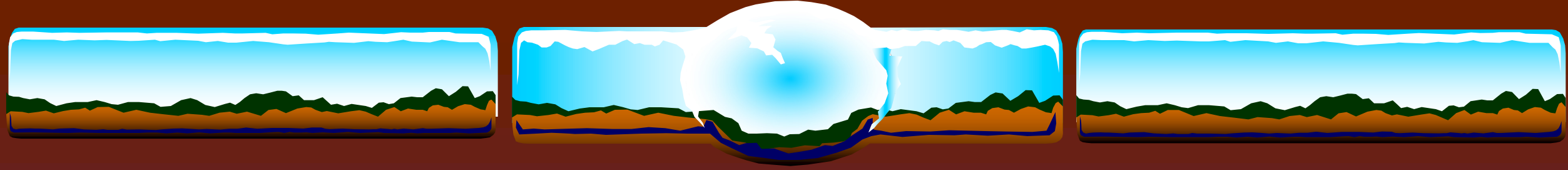


Laboratory diagnosis of Syphilis

Jonathan Vilasier Iralu, MD, MACP, FIDSA

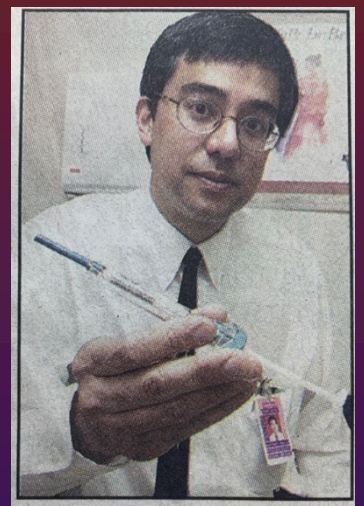
Indian Health Service

Chief Clinical Consultant for

Infectious Diseases

Disclosures

I hate syphilis!



DOUGLAS TESNER
THE ASSOCIATED PRESS

DISEASE FIGHTER: Dr. Jonathan Iralu, of the Gallup Indian Medical Center, holds a syringe of penicillin used to treat syphilis, a disease that is sharply increasing on the Navajo Reservation.

ABQ
Journal
June 2003

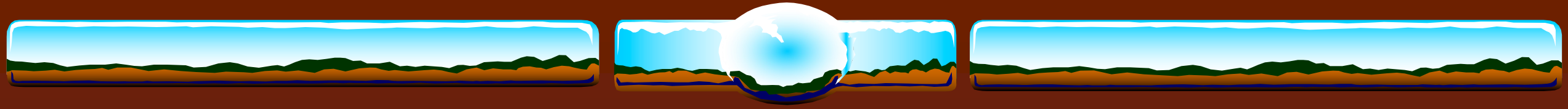
Objectives

At the end of this presentation, participants will be able to:

1. Order the correct diagnostic tests for syphilis diagnosis
2. Understand reverse algorithm testing
3. Use testing to guide management and ensure adequate treatment
4. Increase screening rates in New Mexico

Case Presentation

- A 26 year-old cisgender man walks in to the Express STI Testing Clinic to request a rapid test for syphilis. He has no symptoms and is triaged to go directly to the lab for STI bundle testing. The Treponema pallidum Ab EIA comes back positive and a reflex RPR is positive at a titer of 1:16 dilutions.



Questions to answer…

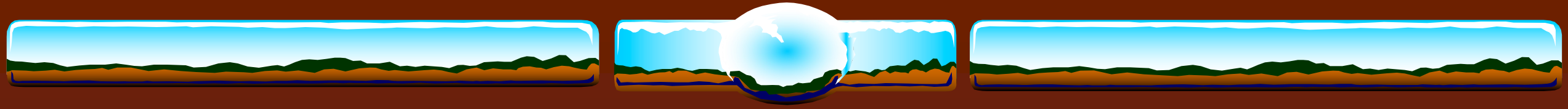
- What do these tests mean?
- Does this man have syphilis?
- What should we do next for him?

Treponema pallidum Structure

- Caused by *Treponema pallidum,* a microaerophillic, corkscrew shaped spirochete bacterium
- Has a cell wall, peptidoglycan layer and a fragile external lipid bilayer with no LPS
- Endoflagella make it rotate and move linearly
- Surface has integral membrane proteins, lipoproteins and phospholipids but these are few and antigenicity is weak

Treponema pallidum Immunology

- Innate immune system is unable to clear this pathogen
- The lack of organism specific antigens helps with this evasion
- Antigens presented by phagocytes are either unique or shared with host cells:
  - Cardiolipin is an integral mitochondrial membrane phospholipid
  - Cholesterol and Phosphatidylcholine are host phospholipids on the syphilis membrane



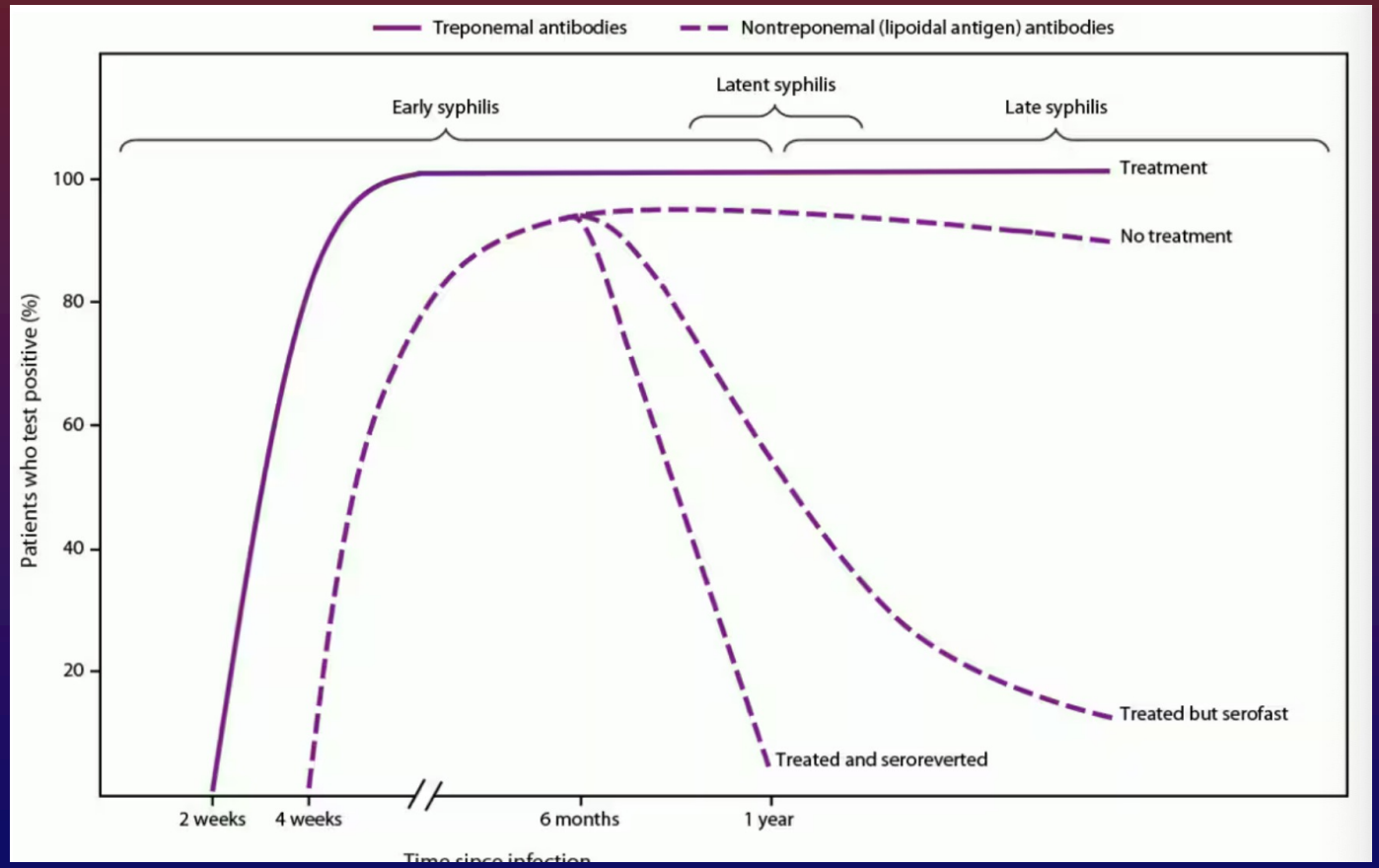
Syphilis stages

- Incubation period 21 days
- Primary syphilis chancre lasts 2-3 weeks
- Secondary syphilis rash with bacteremia starts 2-8 weeks later
- Latent period begins with the end of symptoms and can go for years
- Invasion of the CNS occurs in 30% of early syphilis cases
- Syphilis can reactivate decades after the original infection

Two types of Syphilis Serologic tests

- Nontreponemal → tests that look at those shared human antigens
  - RPR and VDRL
  - Identify lipoidal antigens cardiolipin, phosphatidyl choline, & cholesterol
  - Rise with syphilis infection, other infections and other tissue damage
- Treponemal → tests that look at syphilis antigens
  - Specific antibodies to *Treponema pallidum*
    - H9-1 monoclonal Ab used in DFA
    - Tp47, Tp17, Tp15, and Tp44 used in the EIA assays

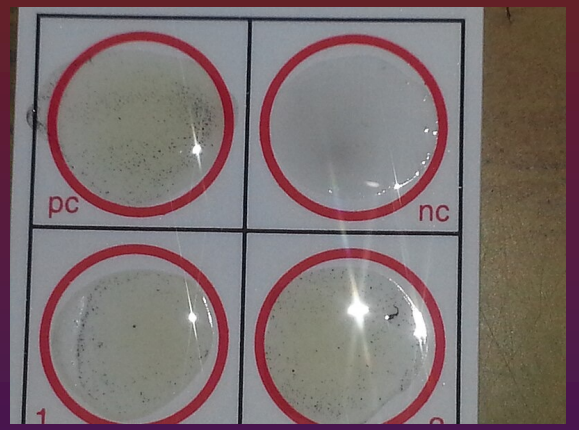
Serologic response to T pallidum infection



Other tests to mention and probably forget

- Dark Field Microscopy (DFM) for skin lesions
  - Requires cumbersome microscope and reagents
- T pallidum direct fluorescent antibody (DFA)
  - Sensitive as DFM but not FDA approved
- Silver stain of tissue biopsies
- T pallidum PCR:
  - Not FDA approved, high sensitivity and specificity for genital ulcers

Nontreponemal test: the RPR



- Rapid Plasma Reagin
  - Manual flocculation test
  - Automated antigen flocculation readers
- RPR was traditionally performed first and confirmed with a treponemal antibody test
- RPR titers are expected to drop fourfold after 12 months for early syphilis and 24 months for late latent syphilis

Nontreponemal test: the RPR

- Two phenomena to be aware of:
  - Prozone (negative RPR but the patient has clinical syphilis)
    - Massive excess of antibody can prevent lattice formation and flocculation yielding a false negative test
    - Remedy is dilution
  - Biologic false positive : (+) RPR but (-) confirmatory treponemal antibody
    - Seen in pregnancy, malaria, leprosy, HIV, recent vaccines, autoimmunity, injection drug use
    - This is not syphilis!

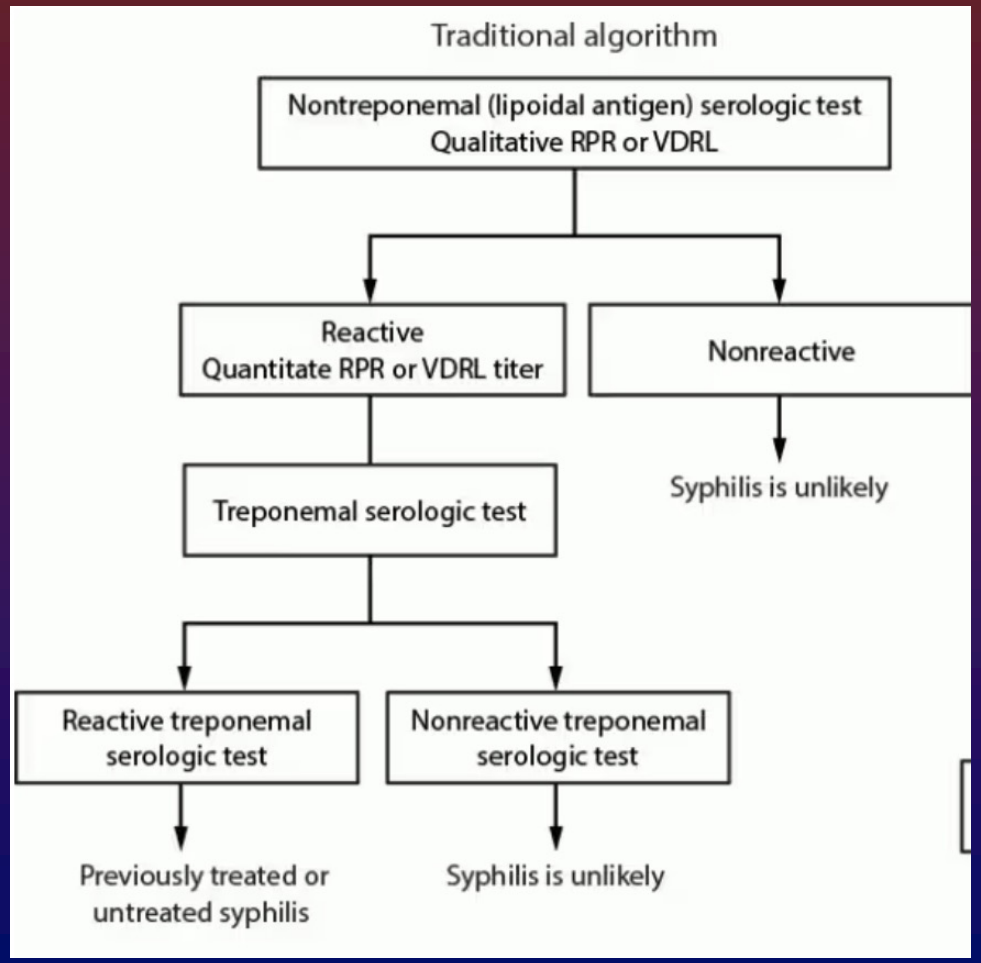
Treponemal Tests

- Detect Treponema pallidum before the RPR rises
- Stay positive for life except in advanced HIV disease
- Common treponemal test include
  - FTA-ABS
  - TPPA (the gold standard)
  - Captia syphilis IgG EIA
  - Trepsure (Labcorp test- proprietary EIA)
  - Zeus scientific EIA
  - Roche Elecsys ECIA (electrochemiluminescence)

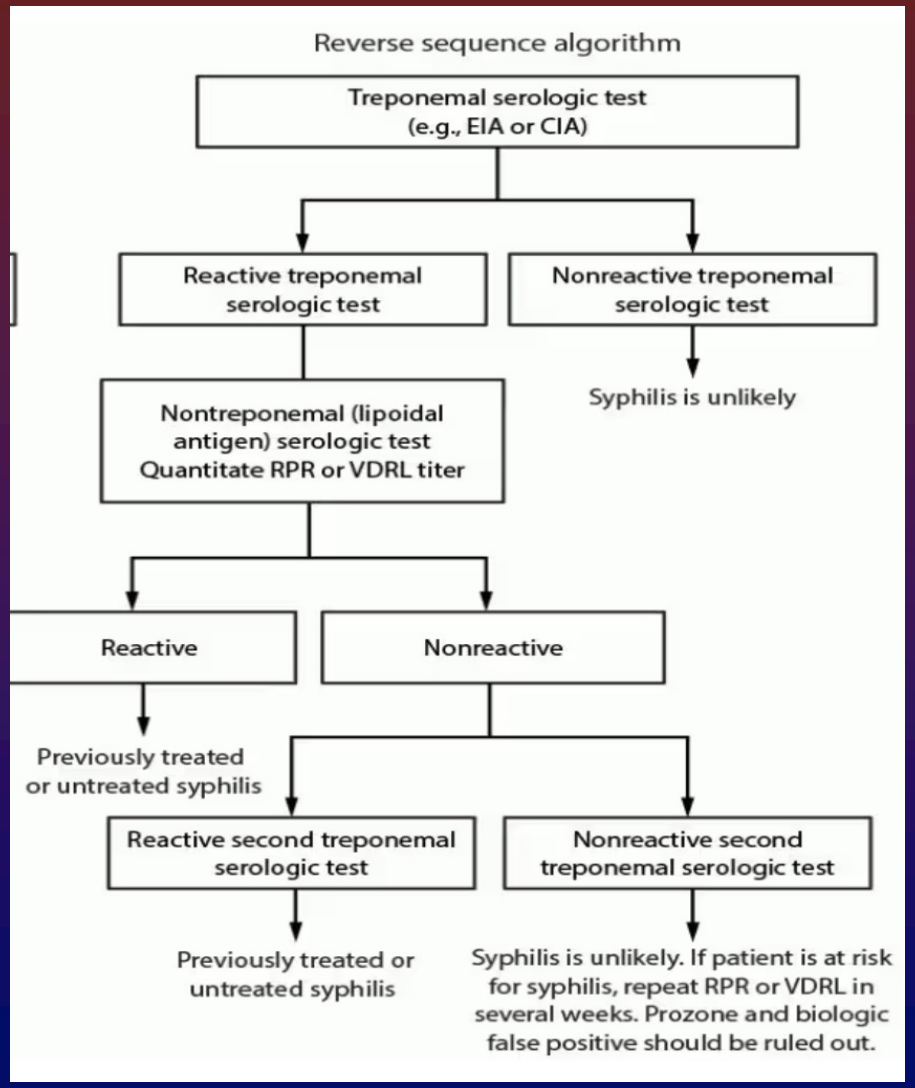
Syphilis Diagnosis

- We used to do the RPR first the reflex to confirmatory TPPA
- Many labs now do an EIA first, then RPR, using the *REVERSE Algorithm*
- Doing EIA first saves money and is quicker
- What to do if RPR is negative?

Traditional algorithm



Reverse algorithm



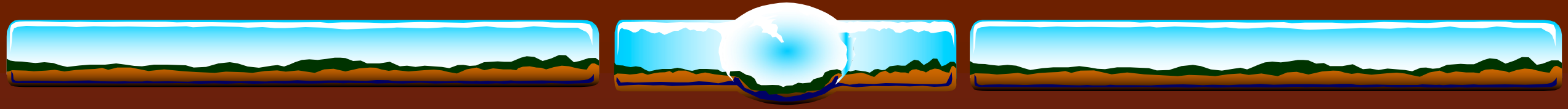
Sensitivity of syphilis tests

	RPR	Treponemal Ab Immunoassays
Primary (vs darkfield)	48.7-92.7%	53.8% (Trepsure)
Secondary	100%	100% (5 EIAs)
Early Latent	82-100%	95-100%
Late Latent	63-66%	91.7-100%

https://www.cdc.gov/mmwr/volumes/73/rr/rr7301a1.htm#F3_down

Specificity of treponemal syphilis tests

- Manual tests
  - TPPA has the best specificity at 95-100% for serology
  - FTA-ABS has lower specificity as a serology but a superior negative predictive value for CSF
- Automated
  - 78.4-86% for most automated tests
  - Trepsure specificity is low at 82.6%



CSF diagnosis of neurosyphilis

- Neurosyphilis is diagnosed clinically with lumbar puncture
  - CSF VDRL positive
  - Protein > 45 mg/dL (some authors recommend 50 mg/dL)
  - WBC >5 cells (some authors use > 20 cells for the HIV positive patient)
- An optional FTA-ABS has a high negative predictive value
  - Off label, not FDA approved

Testing special populations

- Pregnancy
  - Treponemal and non-treponemal tests are interpreted the same as for non pregnant persons
  - If there is a four-fold increase sustained over 2 weeks, there is reinfection
- HIV
  - Treponemal and non-treponemal tests are interpreted the same as for non HIV infected persons
  - Beware of the prozone effect!
  - Follow the titers out for two years

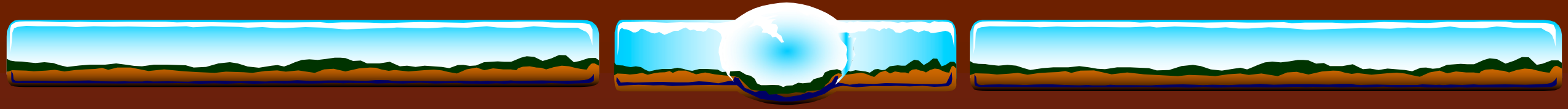
Following patients after treatment

- Early syphilis (primary, secondary, latent < 1 year duration)
  - Check titer at 6 and 12 months
  - A four-fold drop in titer indicates a cure at 12 months
  - A failure to drop four fold warrants HIV testing, careful neuro, eye, ear exam and consideration of treatment for late latent syphilis if negative
  - A sustained four fold rise in titer indicates reinfection
- Late Latent syphilis (>1 year duration)
  - Expect a four fold drop in titer at 24 months to call it a cure

Case Presentation #1

The asymptomatic patient in the initial vignette with an RPR titer of 1:16 receives Benzathine PCN weekly x 3 for late latent syphilis. He returns 6 months later and the titer is 1:8.

What should you do now?



Do the math!

- Calculate the drop: 16/8 = 2-fold drop → No significant change
- Check the timing: 1 vs 2 years
- Conclusion:
  - Wait another year and only act if the two year RPR is not four-fold lower

Case presentation #2

- A 25 year old cis-man who has sex with men has a painful penile ulceration in the Walk In Clinic. The provider suspects herpes simplex and treats the patient with valacyclovir. He reassured when the RPR test comes back negative but is puzzled that the Herpes PCR is also negative .

- The patient comes back 6 weeks later and the ulcer is gone but he has some patchy hair loss and a painful right eye.

What could have gone better…

- Both treponemal and non-treponemal tests have low sensitivity for primary syphilis.

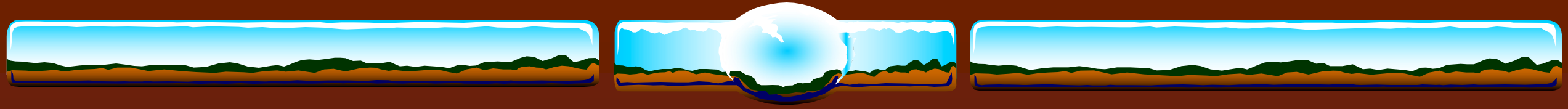
- During a syphilis epidemic, always treat empirically when syphilis is on the differential even if the tests are not congruent:
  - Primary syphilis: serologic testing has low sensitivity, atypical symptoms
  - Prozone effect may be present in secondary syphilis with HIV

Case presentation #3

- A 63 year old cis woman has been acting strange lately according to her daughter who accompanies her to the clinic. She changed from being a fastidious dresser to being less so and now sometimes hears voices and sees little green men in the exam room. On exam she has poor balance and cannot do serial 7s or remember 3 objects after two minutes. You send a B12, TSH, HIV and Syphilis serology and the latter is positive

Case presentation #3

- What should you do next?
  a) Refer for neuropsych testing
  b) Order a STAT MRI
  c) Refer to a neurologist at the University Hospital 130 miles away that has a 6 month wait list
  d) Start donepezil
  e) Do a lumbar puncture



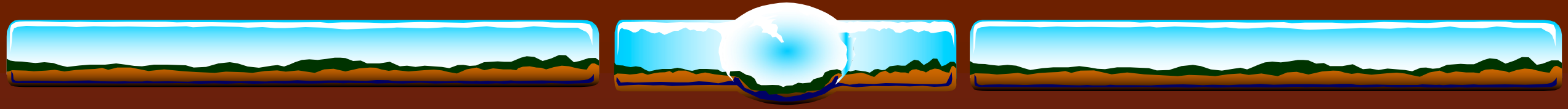
Diagnosing neurosyphilis

- Go for the lumbar puncture!
  - If you sent the syphilis test for neurologic symptoms, you need an LP
  - Consider doing a brain CT or MRI first if there is a possibility of mass or increased intracranial pressure
  - Send the fluid for Cell Counts, Protein and VDRL
  - Consider adding on an FTA-Abs for that high predictive value of a negative test

Case Presentation #4

The original patient's female partner was interviewed shortly after he was diagnosed. She promised to come in to the hospital for blood work and a clinic visit for exam and treatment. She never shows up for this visit despite multiple phone calls over the next 3 months.

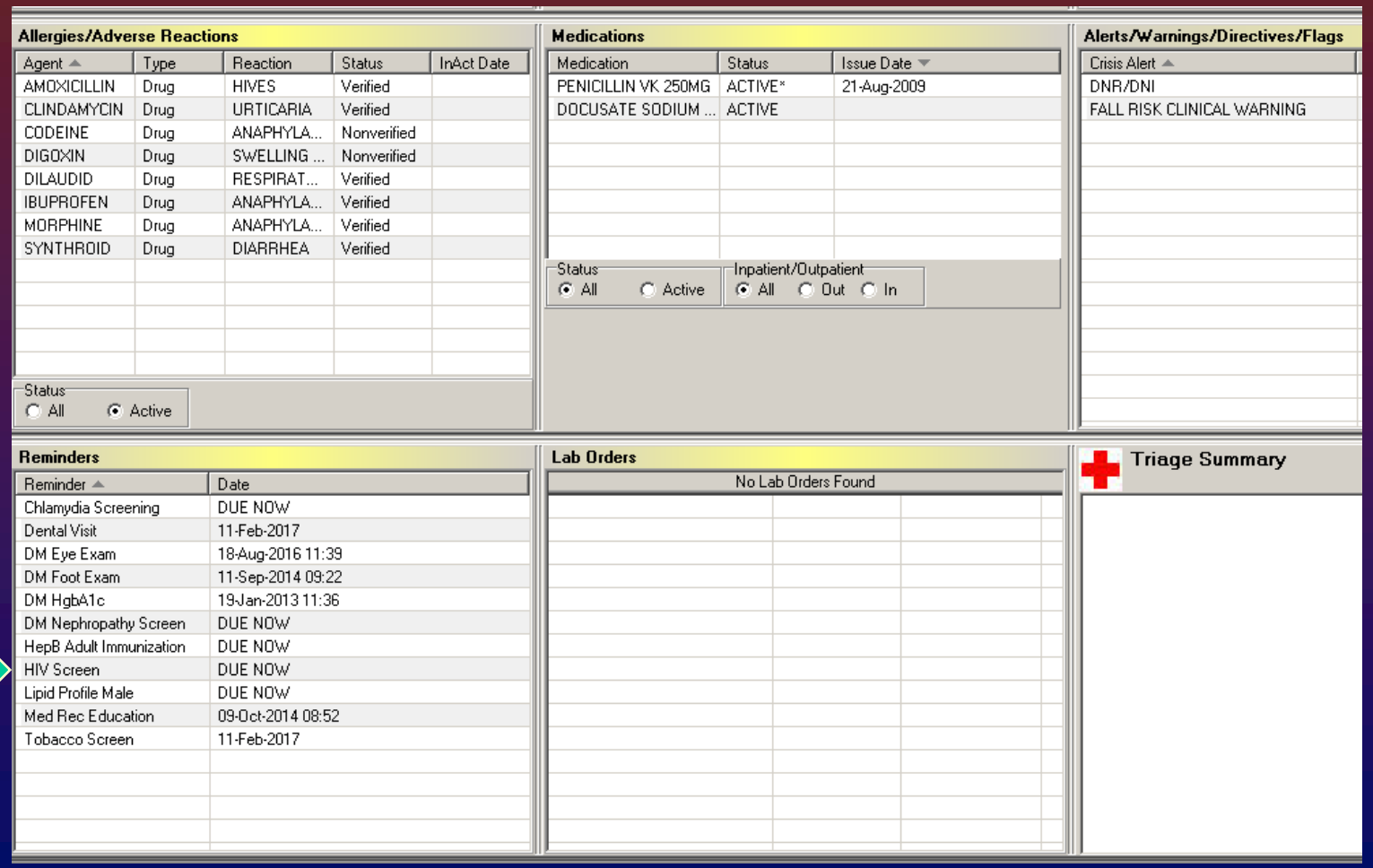
What can be done to prevent this scenario?



The answer is…

Universal, risk based, on-demand or home testing

EHR front page reminders are pretty good ….



Allergies/Adverse Reactions

Agent	Type	Reaction	Status	InAct Date
AMOXICILLIN	Drug	HIVES	Verified	
CLINDAMYCIN	Drug	URTICARIA	Verified	
CODEINE	Drug	ANAPHYLA...	Nonverified	
DIGOXIN	Drug	SWELLING ...	Nonverified	
DILAUDID	Drug	RESPIRAT...	Verified	
IBUPROFEN	Drug	ANAPHYLA...	Verified	
MORPHINE	Drug	ANAPHYLA...	Verified	
SYNTHROID	Drug	DIARRHEA	Verified	

Status: All / Active

Medications

Medication	Status	Issue Date
PENICILLIN VK 250MG	ACTIVE*	21-Aug-2009
DOCUSATE SODIUM ...	ACTIVE	

Status: All / Active
Inpatient/Outpatient: All / Out / In

Alerts/Warnings/Directives/Flags

Crisis Alert
DNR/DNI
FALL RISK CLINICAL WARNING

Reminders

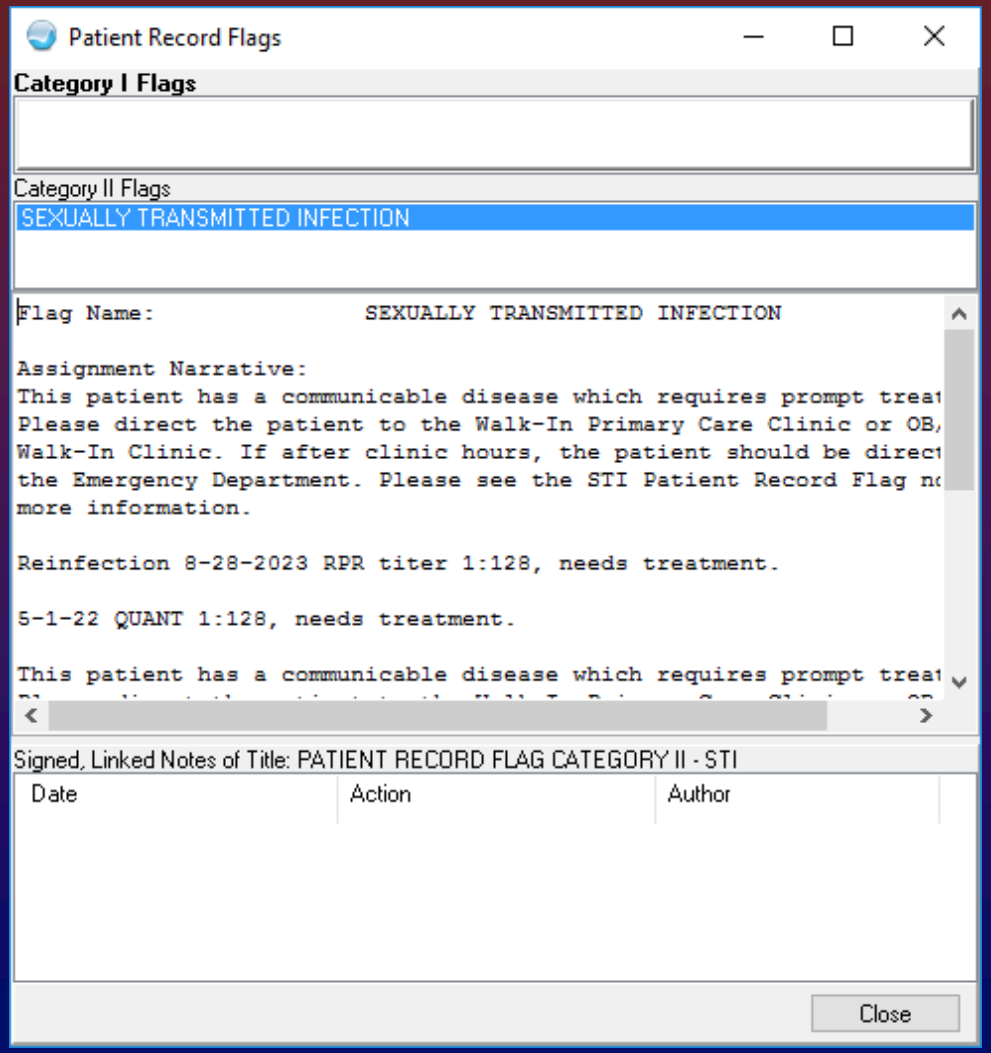
Reminder	Date
Chlamydia Screening	DUE NOW
Dental Visit	11-Feb-2017
DM Eye Exam	18-Aug-2016 11:39
DM Foot Exam	11-Sep-2014 09:22
DM HgbA1c	19-Jan-2013 11:36
DM Nephropathy Screen	DUE NOW
HepB Adult Immunization	DUE NOW
HIV Screen	DUE NOW
Lipid Profile Male	DUE NOW
Med Rec Education	09-Oct-2014 08:52
Tobacco Screen	11-Feb-2017

Lab Orders

No Lab Orders Found

Triage Summary

These POP-UP reminders are WAY better!



Indian Health Service Screening Expansion

- Pregnancy: test at diagnosis, week 24 and delivery
- Universal testing age 13-64 years old annually
  - Look at your local distribution and modify
- Screen all admissions to the hospital
- Screen high risk persons in ED or Walk-in Clinic with STI bundle
  - Substance use disorder
  - Pregnancy
  - GI Bleed or trauma
  - Mental Health Crisis
  - Other STI

Indian Health Service Screening Expansion

- Express STI testing
  - Laboratory based (avoid the clinic)
  - Urgent care with no provider visit unless symptomatic
    - Send directly to lab for STI bundle testing
    - Make telemedicine appointment in 1 week
    - Call patient in sooner if a test is positive
    - Refer for HIV PrEP and Doxy PEP if desired

The GIMC Express Testing clinic

WIPCC HOURS

- Open 7AM to 7PM every day
- Last patient check-in will be at 5:30PM

WIPCC LOCATION

516 E. Nizhoni Blvd
Gallup, NM
87301

Located in the modular building behind the GIMC main hospital.

WIPCC PHONE NUMBER

(505) - 722 - 1253

SERVICES

- "Express" STD testing for patient and partner
- Patient being tested must be without symptoms
- If STD symptoms are present, a clinic visit with a primary care provider may be necessary
- Anyone can walk-in during regular business hours. No appointment necessary.
- Additional clinic referrals are available

STD SCREENING RECOMMENDATIONS

Who should be tested for STDs?

- Sexually active women under 25 years old
- Women and men over 25 years old with risk factors for STDs
- Men who have sex with men
- Transgender Men and Women
- Persons with HIV
- Anyone who would like to be tested

STD risk factors

- Having multiple sex partners
- Recent incarceration
- Transactional sex work
- IV drug use
- Men who have sex with men
- High risk behavior

GALLUP INDIAN MEDICAL CENTER

CDC STD Screening Information

GALLUP INDIAN MEDICAL CENTER

EXPRESS STD TESTING

AVAILABLE AT GIMC WIPCC

Indian Health Service Screening Expansion

- Field Testing with HealthCheck or Chembio DPP test
  - Events: Tribal fair, flea markets, soup kitchens, community pantry, shelters, jails, detox
  - Street Medicine Outreach
  - Partner testing during visits
  - Use incentives to encourage patients to get tested and to come back for follow-up
  - Offer prevention: condoms, lube, Doxy PEP, HIV PrEP

>>Give Field Penicillin immediately if high risk and test positive

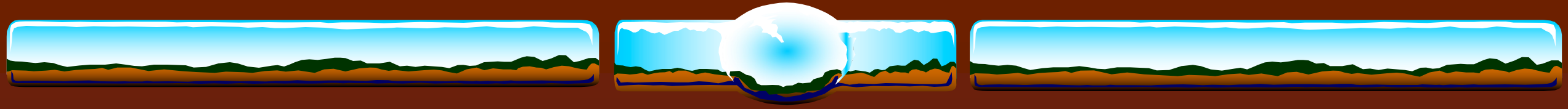
Home Self Testing

INDIGI iwtk™ I WANT THE KIT

Take Control.
Know Your Status.

The new home test option

- FDA just approved the first at home test for OTC use:
  - Now Diagnostics. First To Know
  - An alternate home test for people without internet cell phone access?
  - We need to figure out innovative ways in Indian Country to use this



Take Home Pearls:

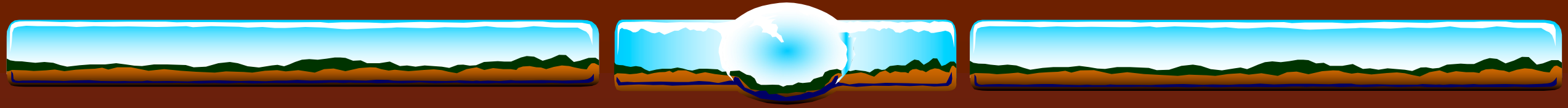
- Screen with T pallidum EIA using the reverse algorithm in 2024
- Treat before the test results come back
- Use the RPR to document a cure (12 months for early, 24 for late)
- Screen outside the box!

References

- Papp JR, Park IU, Fakile Y, Pereira L, Pillay A, Bolan GA. CDC Laboratory Recommendations for Syphilis Testing, United States, 2024. MMWR Recomm Rep 2024;73(No. RR-1):1–32. DOI: http://dx.doi.org/10.15585/mmwr.rr7301a1

- Peeling, R., Mabey, D., Kamb, M. *et al.* Syphilis. *Nat Rev Dis Primers* **3**, 17073 (2017). https://doi.org/10.1038/nrdp.2017.73

Thank you IHS PHNs!



Stomp Out Syphilis!!