ACMG
American College of Medical Genetics and Genomics
Translating Genes into Health®

AMP
Association for Molecular Pathology

IDSA
Infectious Diseases Society of America

What do Cancer Moonshot, PMI, Zika and the CARB National Action Plan All Have in Common?

Briefing on the basics of laboratory developed tests (LDTs) and the vital role they play in patient care

Tuesday, September 20th
3:00 – 4:00 PM

Capitol Visitor Center, SVC 208-09

Presenters

- **Sherri Bale, PhD, FACMG**, Managing Director, GeneDx, Gaithersburg, MD
- **Janina A. Longtine, MD**, Vice Chair, Pathology and Laboratory Medicine, Yale New Haven Hospital; Immediate Past President; Association for Molecular Pathology
- **Marshall Summar, MD, FACMG**, Chief, Division of Genetics and Metabolism, Children's National Medical Center, Washington, DC
- **Angela M. Caliendo**, MD, PhD, FIDSA, Chief, Division of General Internal Medicine, Brown University; Chair, Infectious Diseases Society of America, Diagnostics Task Force
- **Jonathan Nurse**, Director of Government Relations, Infectious Diseases Society of America

Briefing on Laboratory Developed Tests

IDSA, AMP, ACMG Joint Presentation
Sherri J. Bale, PhD, FACMG
Managing Director
GeneDx, Inc.

Testing Patient Samples in a Clinical Lab

Kits (Device)

MiSeqDx Cystic Fibrosis 139-Variant Assay

Kits are sold to end-users

LDT/Ps (Test/Procedure)

Test is performed in the lab that developed and validated it.

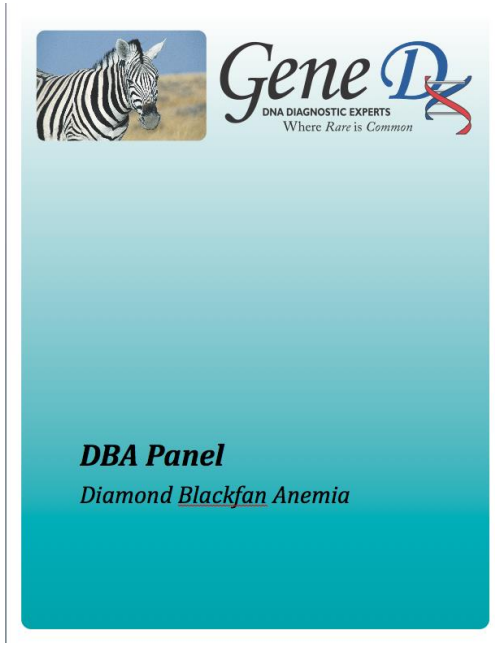
Steps in developing an LDT/P

- Physician/Client Request (genetic test for a specific gene/genes/disorder)
- Knowledge of market need
- Evaluation of *clinical validity*
  - *how well the genetic variant being analyzed is related to the presence, absence, or risk of a specific disease.*
  - Peer-reviewed published papers, public databases, professional society guidelines, etc.
- Compared to *analytical validity*
  - *how well the test predicts the presence or absence of a particular gene or genetic change*.

Developing an LDT

- Determine the most appropriate method for addressing the clinical question
  - Specific variant analysis
  - Full single gene sequencing
  - Sequencing of a panel of relevant genes
  - Sequencing of a whole exome (WES)
  - Sequencing of a whole genome (WGS)
  - Sequencing of the mitochondrial genome
  - Sequencing of RNA
  - Etc.

Approval process for an LDT



Test Readiness Binders

- Assess clinical validity: Justify the choice of genes to be included on a panel. Gather the information about mutation spectrum, gene-phenotype relationship, evaluate test sensitivity using the literature
- Write report templates (pos, neg, inconclusive), Information sheets, web info, test requisition
- Perform technical validation
  - Define required performance characteristics
  - Determine Chemistry and BioInformatic Pipeline
  - Select appropriate control samples (pos and neg)
  - Run-to-run; day-to-day; tech-to-tech reproducibility
  - Evaluate test sensitivity (PPV, NPV of technical approach)
- Write/edit applicable *Standard Operating Procedures* for bench and analysis
- Develop proficiency testing plan

Test Validation-and-Management Documentation

Binder Contents for Panels*

The pathway of the binder is TTV → GC → QS → Lab Ops Dir → QS (Closure Meeting)→ TM

Tabs/Contents/Contributor

Contributors who have the binder please insert documents and also email them to Anne/Sonja.
$ = Signature needed

Gene Specifics
- Final "Technical Details" Sheet ..... QS
- Summary Page: # Genes, # Exons, etc ..... TTV
- Gene List ..... TTV
- Primer List ..... TTV
- Groups and Linker List, if applicable ..... TTV

General SOP
- Overview SOP in effect at the time of test launch ..... QS
- Overview of ExonArray in effect at the time of launch ..... QS

References
- Gene-by-gene bibliography ..... GC

Info sheet or attachment for reports is sufficient, if organized to show which article justifies each gene.

Patient-Physician Information
- Information Sheet ..... GC
- Consent forms if unique ..... GC
- Requisition forms if available ..... GC

Clinical staff also responsible for pricing, LIMS, Genetests, Genedx.com, etc (items not placed in binder)

Sample Reports
- Negative report sample for each panel/subpanel ..... GC
- Positive and VUS reports, if available ..... GC

If we have no Pos/VUS on the new panel yet, but we have samples of Pos and VUS interpretation for these genes that were written for older test platforms, email some saved pdfs from Reports to Anne. Ideally include clearcut/vlm/vlb; het and hom; common and novel; and any "classic" - if applicable.

Validation (Sequencing)
- Lab Readiness Checklist ..... Lab Ops Dir-$
- TTV data tables and report ..... TTV (TTV-$, SJB-$)
- Validation Narrative ..... TTV/Owner (all-$)
- Launch Approval Letter signed by the Managing Director ..... QS (SJB-$)

QS also responsible for notifying CAP and ordering PT if available (these items not placed in binder)

ExonArray
- Checklist signed by the lab's Director of Ops ..... EA Lab
- Validation Narrative and Data, if new ..... EA Lab

Modifications

Test manager insert material on any downstream modifications

Performance

Periodic reviews of how well the test is performing, including the expected vs actual rate of positive results and the TAT.

*To begin a binder, TTV email Sonja with commercial test name including all subpanels, and inside kit/vet name

AM filename: Insert for turquoise "panel" books v. 062714

GeneDx


RESEARCH
ONLY!
RESEARCH
ONLY
No food or drink
PULL
Gene Dx
Gloves
Required
Walkthroughs keep gloves on

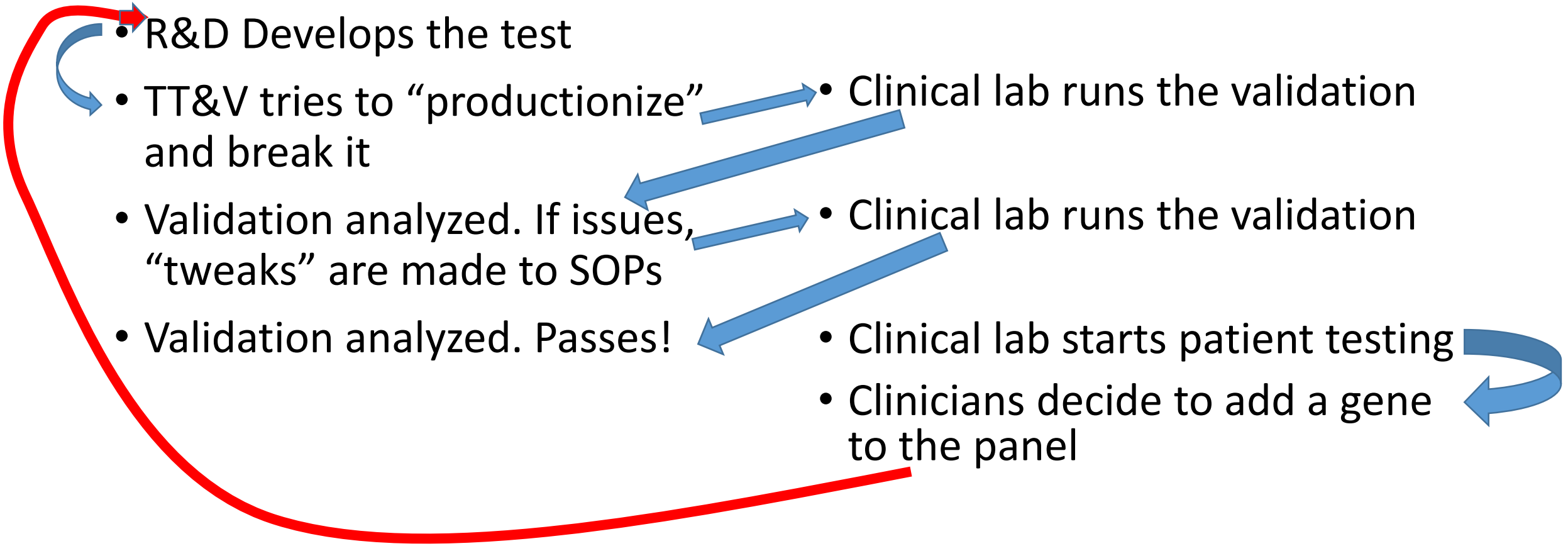
Test Transfer and Validation…
And again…
And yet again

R&D and TT&V Labs

- R&D Develops the test
- TT&V tries to “productionize” and break it
- Validation analyzed. If issues, “tweaks” are made to SOPs
- Validation analyzed. Passes!

Clinical Lab

- Clinical lab runs the validation
- Clinical lab runs the validation
- Clinical lab starts patient testing
- Clinicians decide to add a gene to the panel




SDHD, SDHB SDHC HERED. PARAGANGLIOMA, ETC.
SPINK5 - NTS; ICHTHYOSIS LINEARIS CIRCUMFLEXA
SOX9 - CAMPOMELIC DYSPLASIA
SOX2 - DEVELOPMENTAL EYE DISORDERS
SIX1 - BRANCHIOOTORENAL/BO SYNDROME
SHH SIX3 TGIF ZIC2 Holoprosencephaly
SH3BP2 - CHERUBISM
SGSH - N-sulfoglucosamine Sulfohydrolase
SMPD1 - NIEMANN PICK DISEASE
SMC1A - Structural Maintenance of Chromosomes 1A
SMAD4 - SMAD FAMILY MEMBER 4
SLC9A6 - ANGELMAN SYNDROME (AS)
SLC27A4 - Solute Carrier 27 (Fatty Acid Transporter), Member 4
SLC26A4 - Solute carrier family 26, member 4
SLC25A13 - CITRIN DEFICIENCY
SLC22A5, SLC25A20 - CARNITINE DEFICIENCY
SLC17A5 - SOLUTE CARRIER FAMILY 17
TMEM127 - Transmembrane Protein
TINF2 - DYSKERATOSIS CONGENITA
TH - TYROSINE HYDROXYLASE DEFICIENCY
TGM1 - CONGENITAL RECESSIVE ICHTHYOSIS
TGFBR2 - Transforming Growth Factor, Beta Receptor, 2
TGFBR1 - Transforming Growth Factor, Beta Receptor, 1
TERT - TELOMERASE REVERSE TRANSCRIPTASE
TERC (hTR) - DYSKERATOSIS CONGENITA
TCOF1 - TREACHER-COLLINS-FRANCESCHITTI SYNDROME 1
TBX5 - HOLT ORAM SYDROME
TBX1 - VELOCARDIOFACIAL & DIGEORGE SYNDROMES
TAT - TYROSINEMIA TYPE II
SUMF1 - SULFATASE MODIFYING FACTOR 1
SUFU - suppressor of fused homolog (Drosophila)
STRA6 - DEVELOPMENTAL EYE DISORDERS
STK11 - PEUTZ JEGHERS SYNROME
STAT3 - HYPER IgE SYNDROME
SRY - GONADAL DYSGENESIS
SRD5A2 - 5-α REDUCTASE DEFICIENCY
SPRED1
NA Sequencing Manual
ZRS - ZPA (ZONE OF POLARIZATION ACTIVITY) ETC.
XLRS1 - X-LINKED JUVENILE RETINOSCHISIS
WNT10A -ECTODERMAL DYSPLASIA
WAS: WISKOTT-ALDRICH SYNDROME
VHL - VON HIPPEL-LINDAU SYNDROME
V2X2 - ANOPHTHALMIA; MICROPHTHALMIA
USH2A - arRP/SPORADIC RP; USHER SYNDROME
UNG - URACIL-DNA GLYCOSYLASE
UBE3A - ANGELMAN & ANGELMAN-LIKE SYNDROMES
TSPAN12 - TETRASPANIN 12
TTR - TTR; FAP & CARDIAC AMYLOIDOSIS
TREX1 - ALCARDI-GOUTIERES SYNDROME
TPP1 - TRIPEPTIDYL PEPTIDASE I
TP63 - EEC; SHFM4; HWS; LMS
TP53: Tumor Protein p53
TNFRSF6 - ALPS 1A
TNFRSF1A - FAMILIAL HIBERNIAN FEVER (TRAPS)

Regulatory

- Submit the validation, SOPs, full documentation to:
  - CLIA (Administered by CMS)
  - CAP (College of American Pathologists)
  - NYSDOH (NY State Dept of Health)

Components of CLIA regulation

- Level of complexity of tests performed (most LDTs are moderate or high complexity, particularly the genetic/molecular tests)
- Standards for laboratory personnel (education and certification; training and documentation of competency)
- QC
- QA and patient test management
- PROFICIENCY TESTING

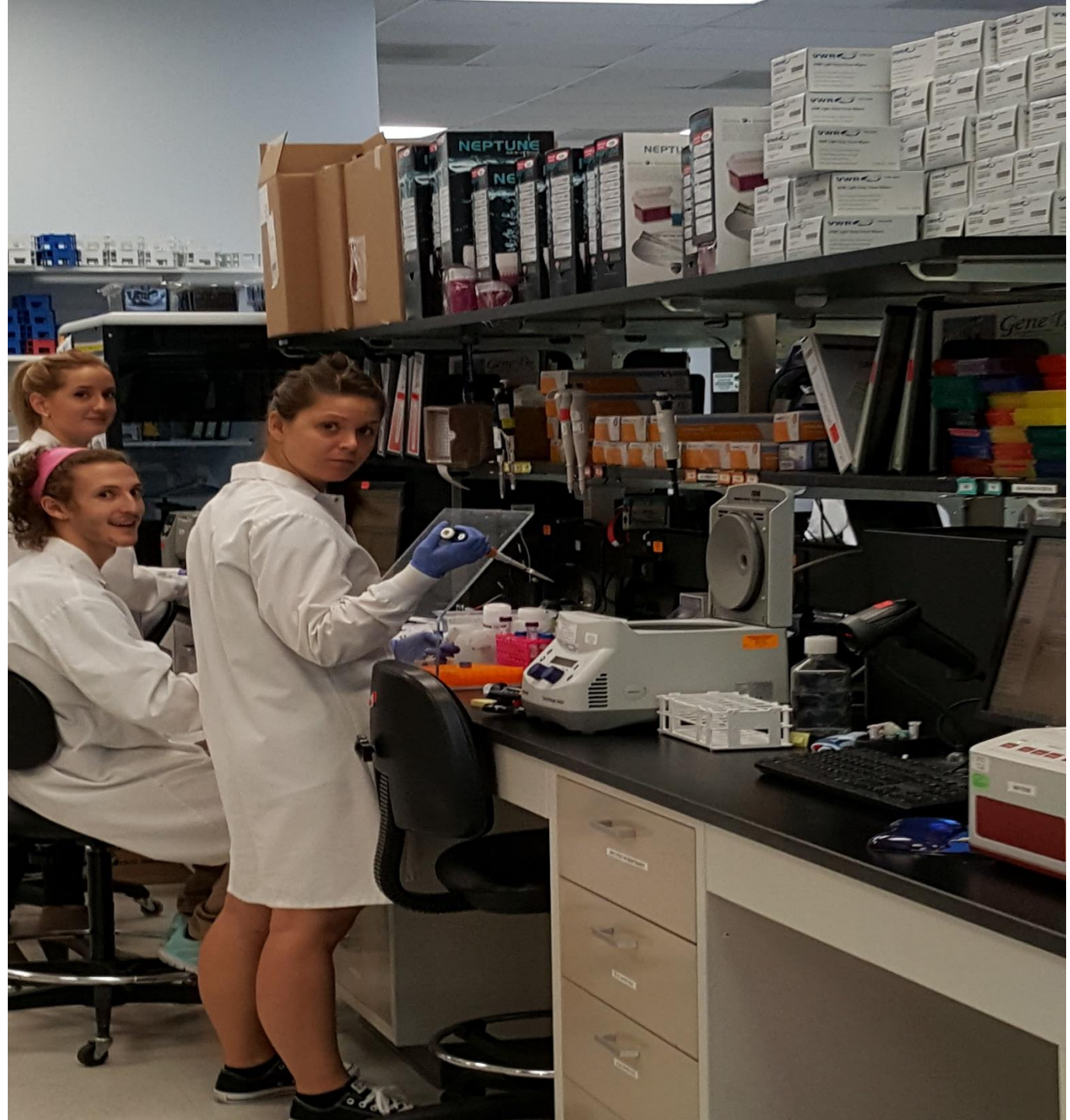
Proficiency Testing

- Each “analyte” must undergo a proficiency test 3 times annually, with 5 samples per testing event
- End to end test
  - Blinded sample from accessions to reporting
  - If an approved proficiency testing program exists for an analyte, the lab must enroll (CAP has many; there are international and other independent programs available). If none is available, the Compliance dept of the lab selects blinded samples from the inventory and send through for end-to-end testing. All results of PT must be documented and available for review upon inspection by CLIA (and other certifying agencies)
  - CMS has authority to impose sanctions for lab’s failure to enroll or poor performance.
  - At any given time, likely 50 or more PT samples are in our lab

What actually happens in the lab?

A little tour of the highlights


FLAMMABLE
INFLAMMABLE
INFLAMMABLE
FedEx
Express


NEPTUNE


Rack 4949
Rack 4950
Rack 4951
Rack 4952
Rack 4953
Rack 4929
Rack 4930
Rack 4931
Rack 4909
Rack 4910


CART B
TRAY #803
1507251-1507500
TRAY #804
1509501-1509750
TRAY #805
1507751-1508000
TRAY #806
1508001-1508250
TRAY #807
1508251-1508500
TRAY #808
1501-1508750
TRAY #809
508751-1509000
TRAY #810
1509001-1509250
TRAY #811
1509251-1509500
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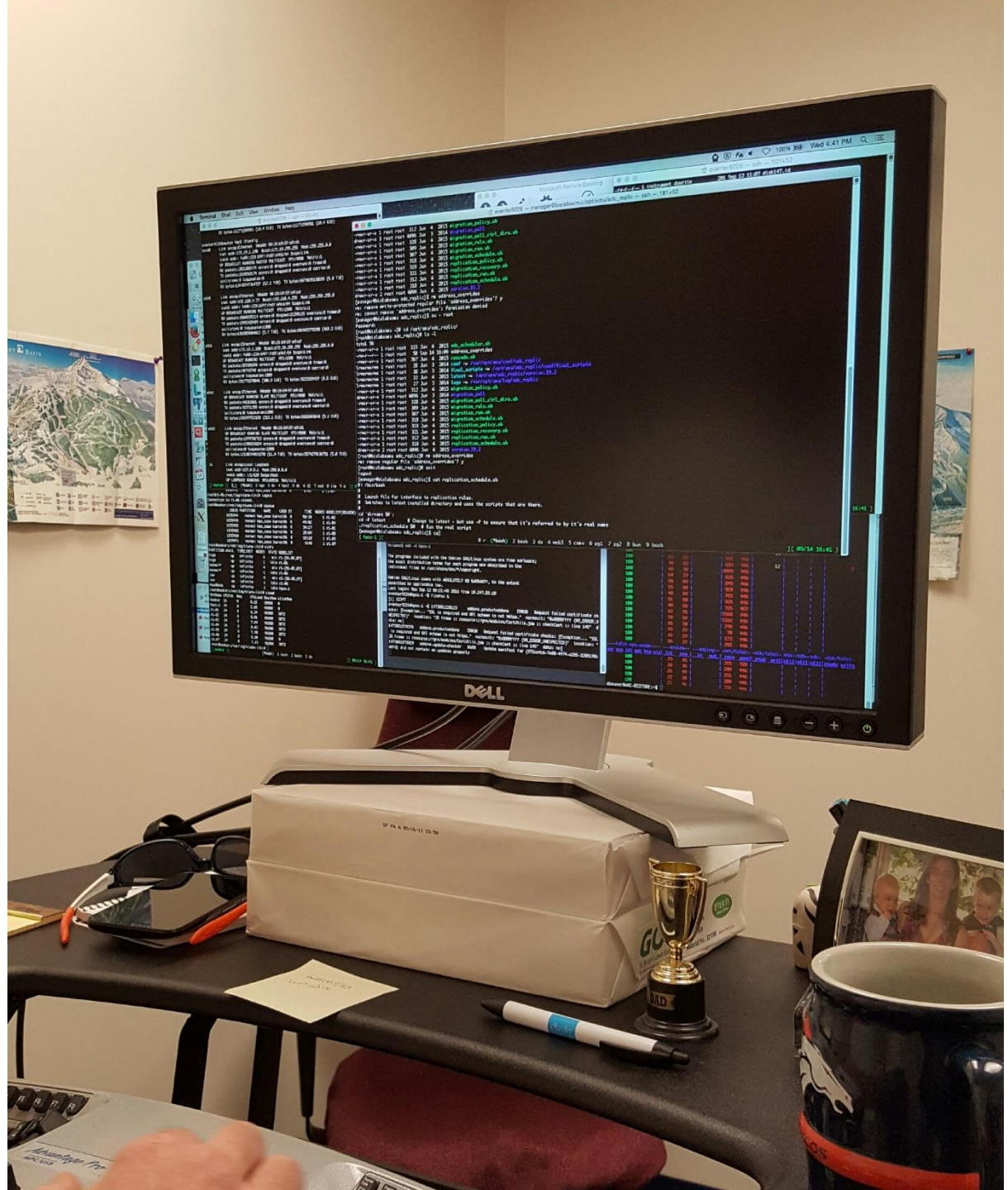
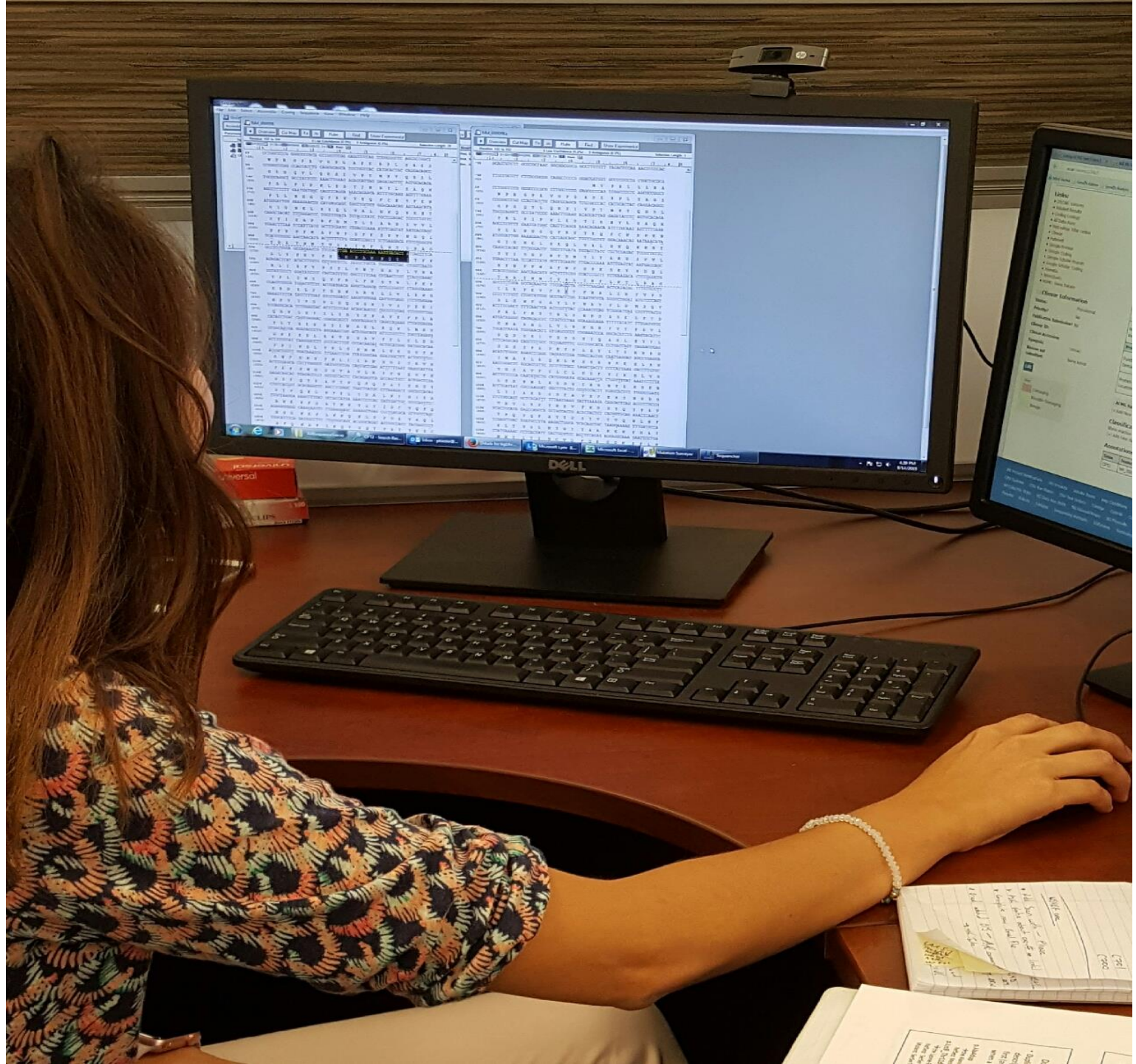

DELL


Mixed
Paper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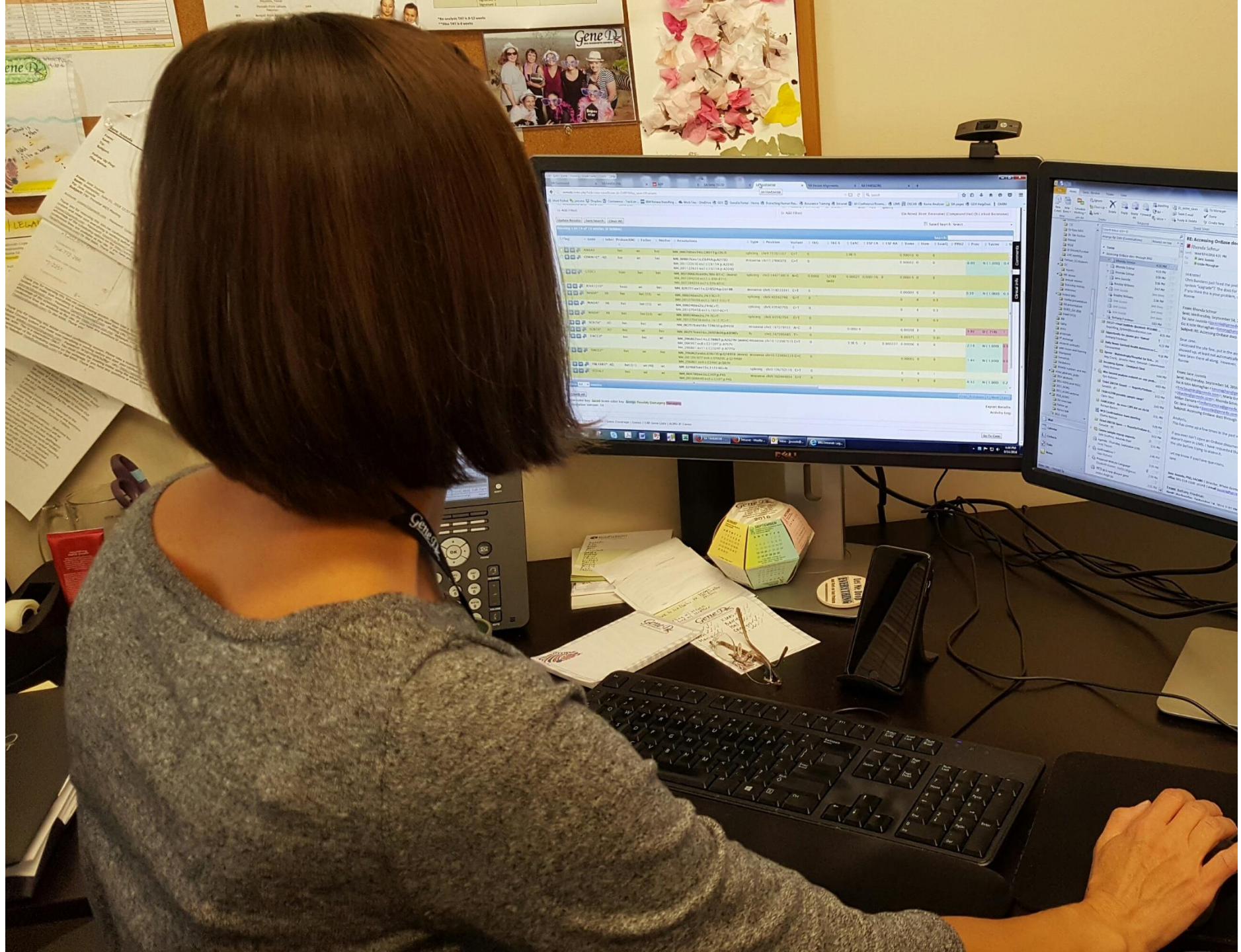


THANK YOU
AUGUST
Hawaiian Host
CARAMELS

Costs incurred in validation of each LDT

- R&D
- TT&V
- End-to-end validations
- Compliance personnel
- Documentation management (training, competency, SOPs, validation documents)
- Proficiency Testing
- Maintaining multiple certifications (CLIA, CAP, NYSDOH, MD, MA, FL, CT, PA)
- Multiple regular inspections from the different agencies
- Documentation and reporting

Economic Impact on additional LDT regulation

- Current Process (CLIA,CAP, NYSDOH)
  - Time to develop, validate, bring to market – 4-6 months, faster if needed
  - Cost to develop, validate, bring to market – $50K- $100K (GeneDx)
- PMA Submission (FDA) (estimates)
  - Time to develop, validate, bring to market – 2.5-4 years
  - Cost to develop, validate, bring to market - $2.5M - $5M per test
- 510K Submission (FDA)(estimates)
  - Time to develop, validate, bring to market – 1 – 1.5 year
  - Cost to develop, validate, bring to market - $50K - $250K per test

Economic Impact, Cont.

- GeneDx, some 500 individual tests
  - FDA regulation would add an addition ~$300M to validation costs
- Smaller labs will not have the resources (personnel or financial)
- Many smaller, concierge, and academic labs are likely to close
- Lack of sites for training of lab geneticists
- Results in loss of innovation, options for patients/physicians
- Slow down in development of new tests
- Consolidation of the largest labs, likely only 4 or so remaining

Laboratory Developed Tests (LDTs) in Oncology

Janina Longtine, MD

Immediate Past President - Association for Molecular Pathology

Vice Chair, Pathology and Laboratory Medicine, Yale New Haven Hospital

Expertise that advances patient care through education, innovation, and advocacy.

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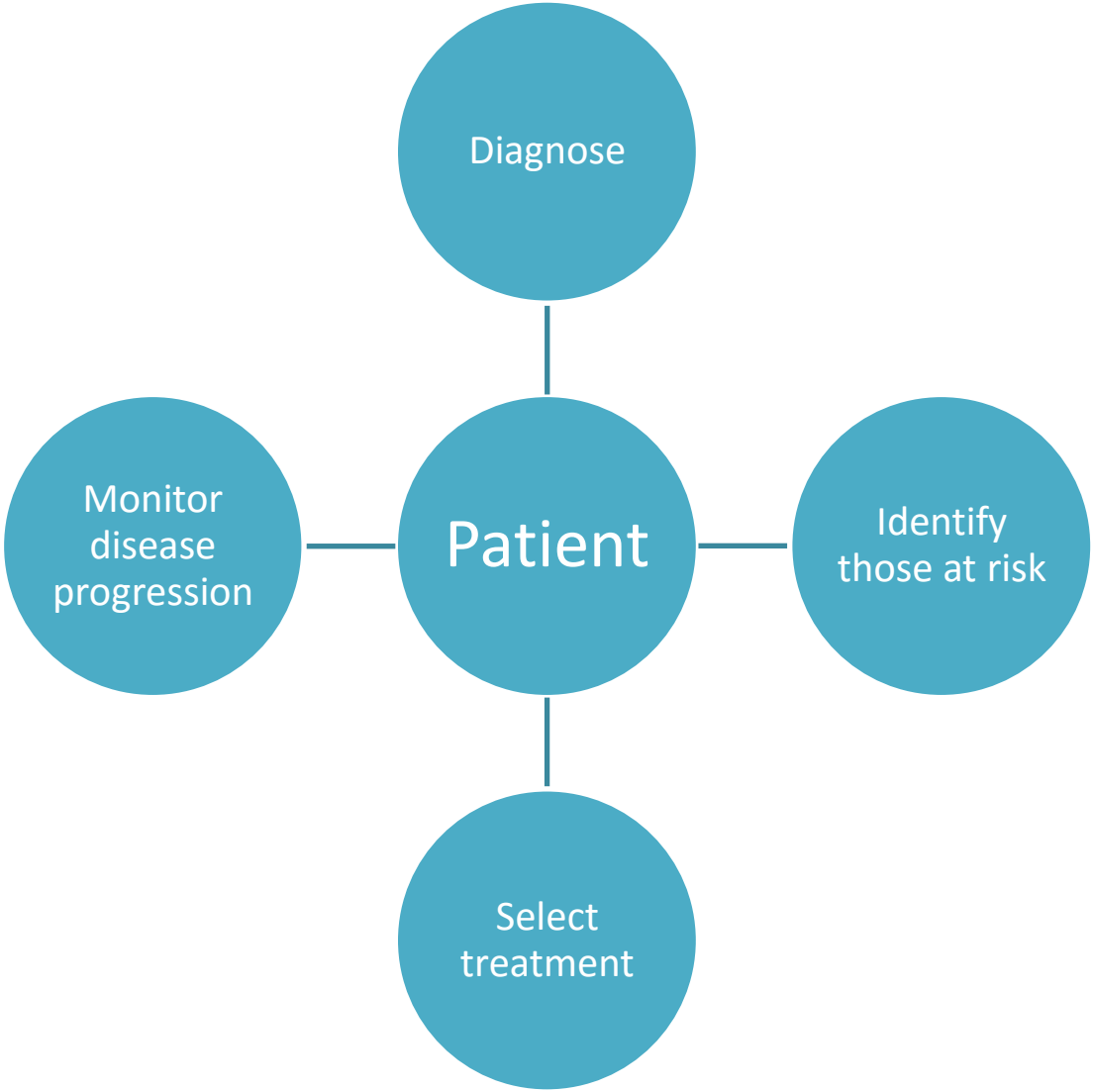
LDTs in Oncology



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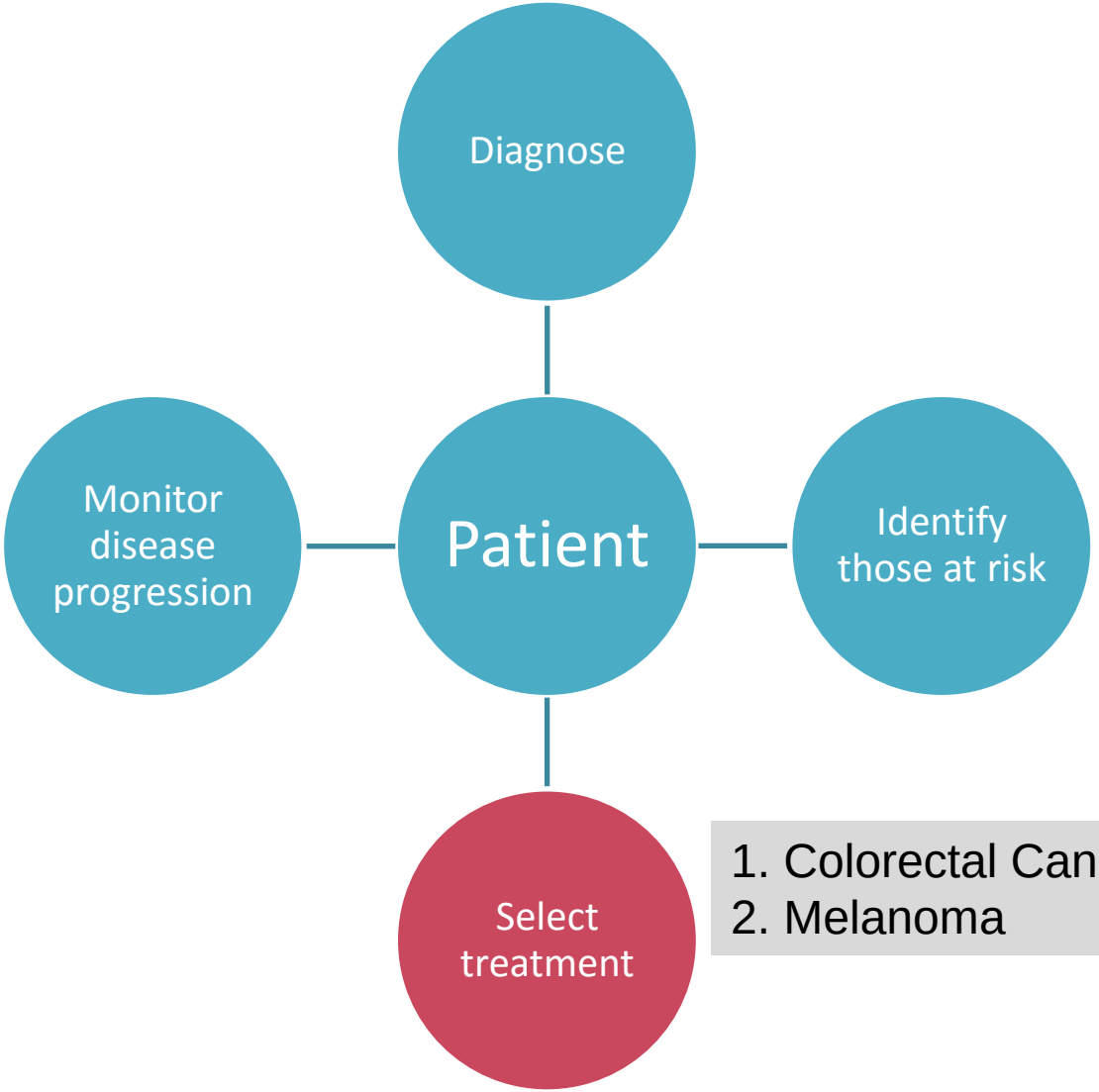
LDTs in Oncology



1. Colorectal Cancer
2. Melanoma

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LDTs Fill Gaps in FDA Approved/Cleared Oncology Tests

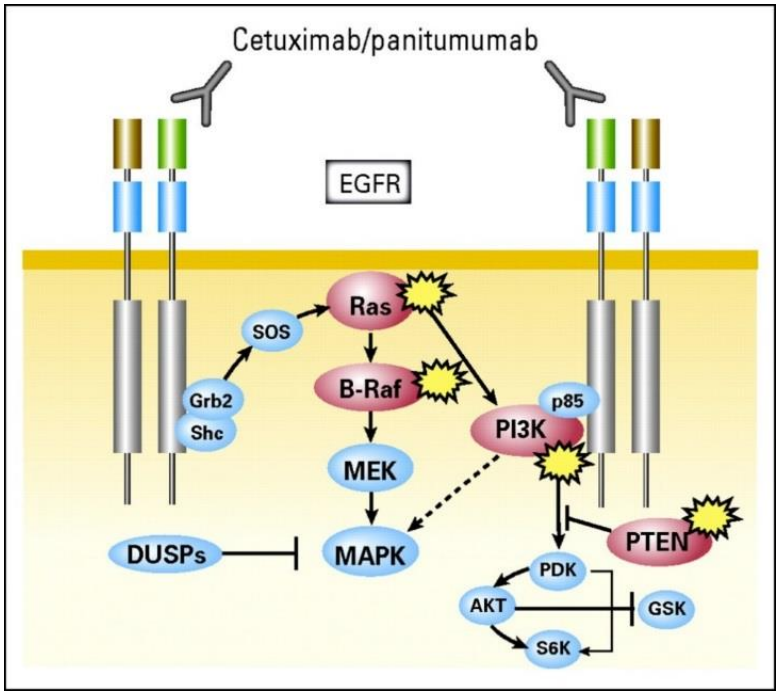
- IVDs:
  - Unable to add newly discovered genetic changes, *i.e.,* mutations, to tests
  - May not be comprehensive and test for all known genetic changes
  - Technology chosen may be limited and unable to detect all types of mutations of interest

→ In many oncology cases, LDTs are standard of care

RAS Mutation Testing in Colon Cancer

RAS mutation testing is essential for determining resistance to EGFR inhibitor therapies used for the treatment of metastatic colon cancer.

- The National Comprehensive Cancer Network (NCCN) evidence-based guidelines recommend genetic testing of colon tumors
- If a patient's tumor tissue is positive for specific RAS mutations, then the patient will not respond to specific therapies.
- RAS testing ensures that patients are not treated with ineffective, expensive, and potentially dangerous drugs.
- The preferred testing uses next generation sequencing, which can detect all therapeutically significant RAS mutations in a single test, in addition to assessing for mutations in other relevant genes.



Bardelli A, Siena S.J Clin Oncol 2010;28:1254-1261

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Oncology Practice Guidelines Urge Comprehensive Testing of RAS Mutations

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2016
Colon Cancer

NCCN Guidelines Index
Colon Cancer Table of Contents
Discussion

PRINCIPLES OF PATHOLOGIC REVIEW (4 of 5)

***KRAS*, *NRAS*, and *BRAF* Mutation Testing**

- **All patients with metastatic colorectal cancer should have tumor tissue genotyped for *RAS* (*KRAS* and *NRAS*) and *BRAF* mutations. Patients with any known *KRAS* mutation (exon 2 or non-exon 2) or *NRAS* mutation should not be treated with either cetuximab or panitumumab.[43,44,45] Evidence increasingly suggests that *BRAF V600E* mutation makes response to panitumumab or cetuximab highly unlikely, as a single agent, or in combination with cytotoxic chemotherapy.[46-48]**
- **Testing for *KRAS*, *NRAS*, and *BRAF* mutations should be performed only in laboratories that are certified under the clinical laboratory improvement amendments of 1988 (CLIA-88) as qualified to perform *high complexity* clinical laboratory (molecular pathology) testing. No specific methodology is recommended (eg, sequencing, hybridization).**
- **The testing can be performed on formalin-fixed paraffin-embedded tissue. The testing can be performed on the primary colorectal cancers and/or the metastasis, as literature has shown that the *KRAS*, *NRAS*, and *BRAF* mutations are similar in both specimen types.[49]**

Microsatellite Instability (MSI) or Mismatch Repair (MMR) Testing

- **Lynch Syndrome tumors screening (ie, IHC for MMR or PCR for MSI)* should be pe… …er diagnosed at age ≤70 y and also those >70 y who meet the Bethesda guidelines.[50] See NCCN … …ssessment: Colorectal**
- **The presence of a BRAF V600E mutation in the setting of MLH1 absence would preclude the diagnosis of Lynch Syndrome.**
- **MMR or MSI testing should also be performed for all patients with stage II disease, because stage II MSI-H patients may have a good prognosis and do not benefit from 5-FU adjuvant therapy. [51]**
- **MMR or MSI testing should also be performed for all patients with metastatic disease.**

***KRAS* exons 2, 3 and 4**
***NRAS* exons 2, 3 and 4**

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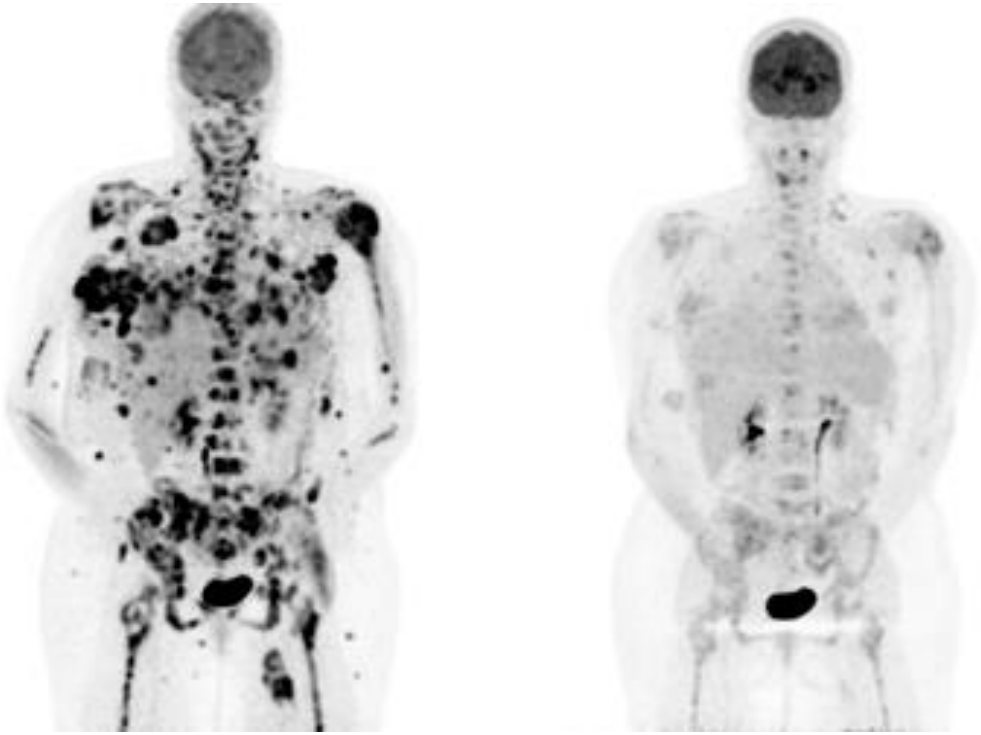
BRAF Mutations in Melanoma

Study of Vemurafenib in Previously Untreated Patients with Metastatic Melanoma



BRAF p.V600 mutation

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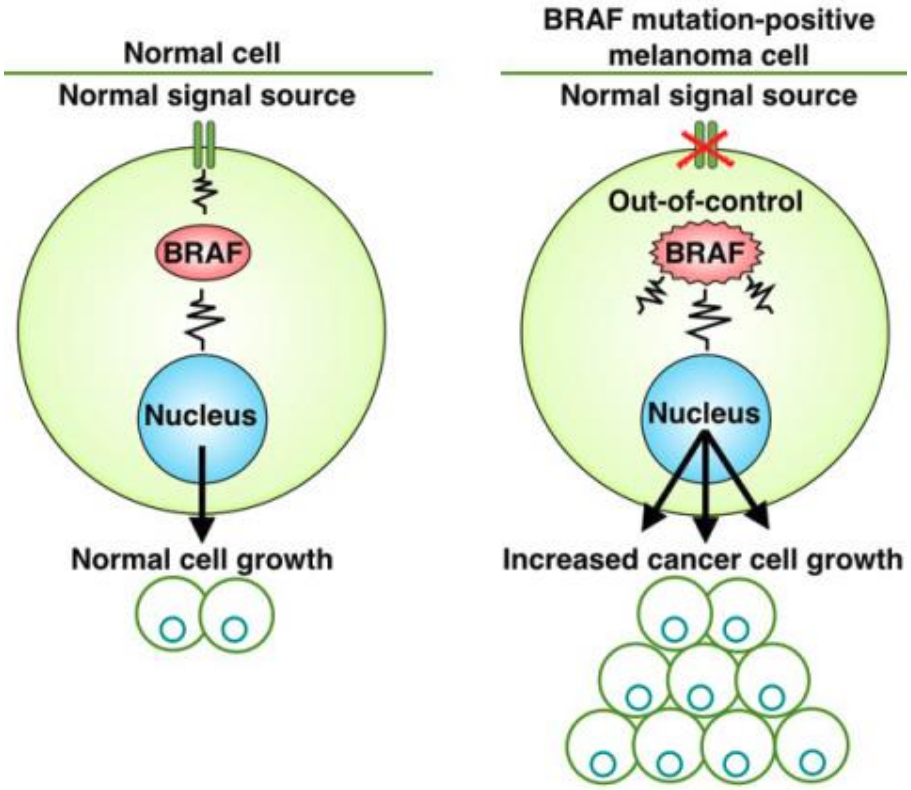
BRAF Mutations in Melanoma

- Melanoma tumors are tested for mutations in the BRAF gene and if present, patients are eligible for new precision medicine therapies
- Unfortunately, the FDA approved tests do not identify all of clinically relevant mutations. Hence, labs prefer LDTs using different technologies.



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Thank You

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HOW LDTS ARE USED IN INFECTIOUS DISEASES

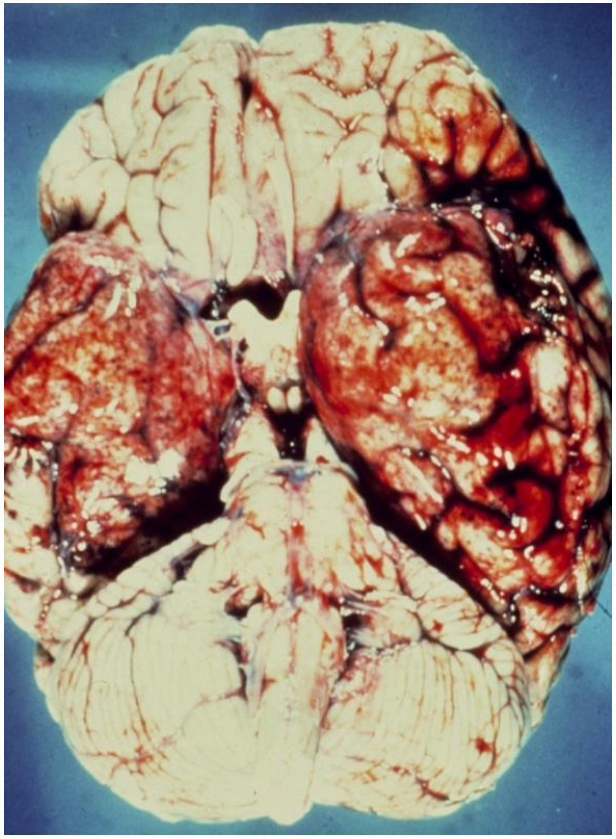
Angela M Caliendo, MD, PhD
Professor and Vice Chair, Department of Medicine
Alpert Medical School of Brown University
Chair, IDSA Diagnostics Task Force
Providence, RI
September 20, 2016

LDTs and Infectious Diseases

- LDTs have been used to diagnose and manage a variety of infectious diseases (ID) since the mid 1990s
- We have a great deal of experience with these tests, they are well designed and validated for reliable use in patient care
- For many infections, LDTs – are the diagnostic standard of care
  - They also provide local, rapid testing for patients
  - In ID patient care time is of the essence; without local testing, sending samples out for testing may take several days
- We often develop LDTs because there are no commercial tests available
  - Labs often switch once several commercial tests become available
  - Many examples of LDTs improving clinical care

Herpes Simplex Virus (HSV) Encephalitis

- Serious infection of the brain
  - High morbidity if not diagnosed and treated quickly
- We have known since 1996 that testing the spinal fluid for HSV DNA is just as good as a brain biopsy
  - Spinal fluid is less invasive and much easier to collect, with lower risk of complications to the patient
  - Molecular tests (PCR) for HSV DNA are much faster and less expensive
- Molecular HSV LDTs were first developed and used clinically

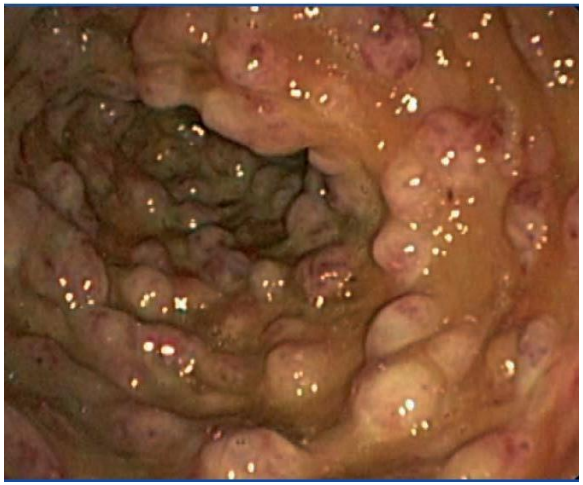


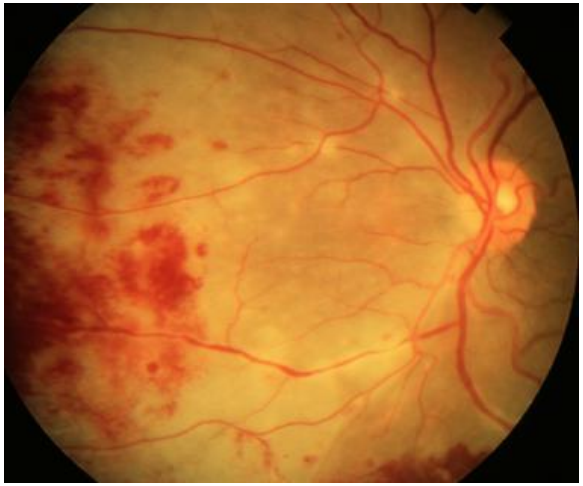
Herpes Simplex Virus (HSV) Encephalitis

- Two commercial tests have been cleared by the FDA, in 2014 and 2015
- Without LDTs we would have performed unnecessary brain biopsies for ~20 years!
- While it is a rare disease, without LDTs we would have also been forced to treat all patients suspected for this infection
- The availability of this LDT improved the management of this infection and prevented thousands of patients from having a brain biopsy

Cytomegalovirus (CMV)

- CMV is a very common viral infection in patients receiving organ and bone marrow transplants
- Diagnosis historically relied on culturing the virus from blood
  - Not very sensitive: more than 50% of cases were missed
  - Led to serious infections involving the brain, colon, esophagus, liver, eye.
- 20 years of research has shown that molecular tests are superior
  - More sensitive, much more rapid, and can measure the amount of virus in the blood (viral load testing)





Cytomegalovirus (CMV)

- US transplant centers have been using viral load testing LDTs for CMV and other transplant associated viruses (BK virus) for years.
- These tests have improved our ability to diagnose infections, and to monitor response to therapy.
- This leads to better outcomes from CMV disease and reduced cases of BK renal infection in kidney transplants.
- There are no FDA approved/cleared BK viral load tests, there are two CMV tests that were only approved in the past two years.
  - Without LDTs this testing would not be possible!

Emerging Infectious Diseases

- Emerging Pathogens are occurring with increasing frequency
  - Zika virus this year
  - The Ebola virus disease outbreak of 2014-2015
  - Enterovirus D68 reemergence in 2014
  - The 2009 influenza pandemic

Emerging Infectious Diseases

- LDTs are a critical mechanism for public health laboratories to rapidly respond to the need for new diagnostics.
  - In outbreaks, speed is necessary to contain an outbreak
  - LDTs can be developed and deployed rapidly in outbreaks, sometimes more rapidly than commercial tests.
  - During the 2009 H1N1 outbreak many local hospitals relied on LDTs to diagnose and guide treatment of patients

Summary

- LDTs are essential for the practice of infectious diseases
- They have a long history of safe and effective use in clinical care
- Lack of LDTs could limit access to high quality testing, that have led to improved management and outcomes of infectious diseases.

https://www.idsociety.org/Diagnostics/

Maintaining Life-Saving Testing for Patients with Infectious Diseases:

Recommendations on the Regulation of Laboratory Developed Tests

PEDIATRIC INFECTIOUS DISEASES SOCIETY

SHEA The Society for Healthcare Epidemiology of America

hivma hiv medicine association

IDSA

The State of Play: Current Proposals to Regulate Laboratory Developed Tests

Jonathan Nurse
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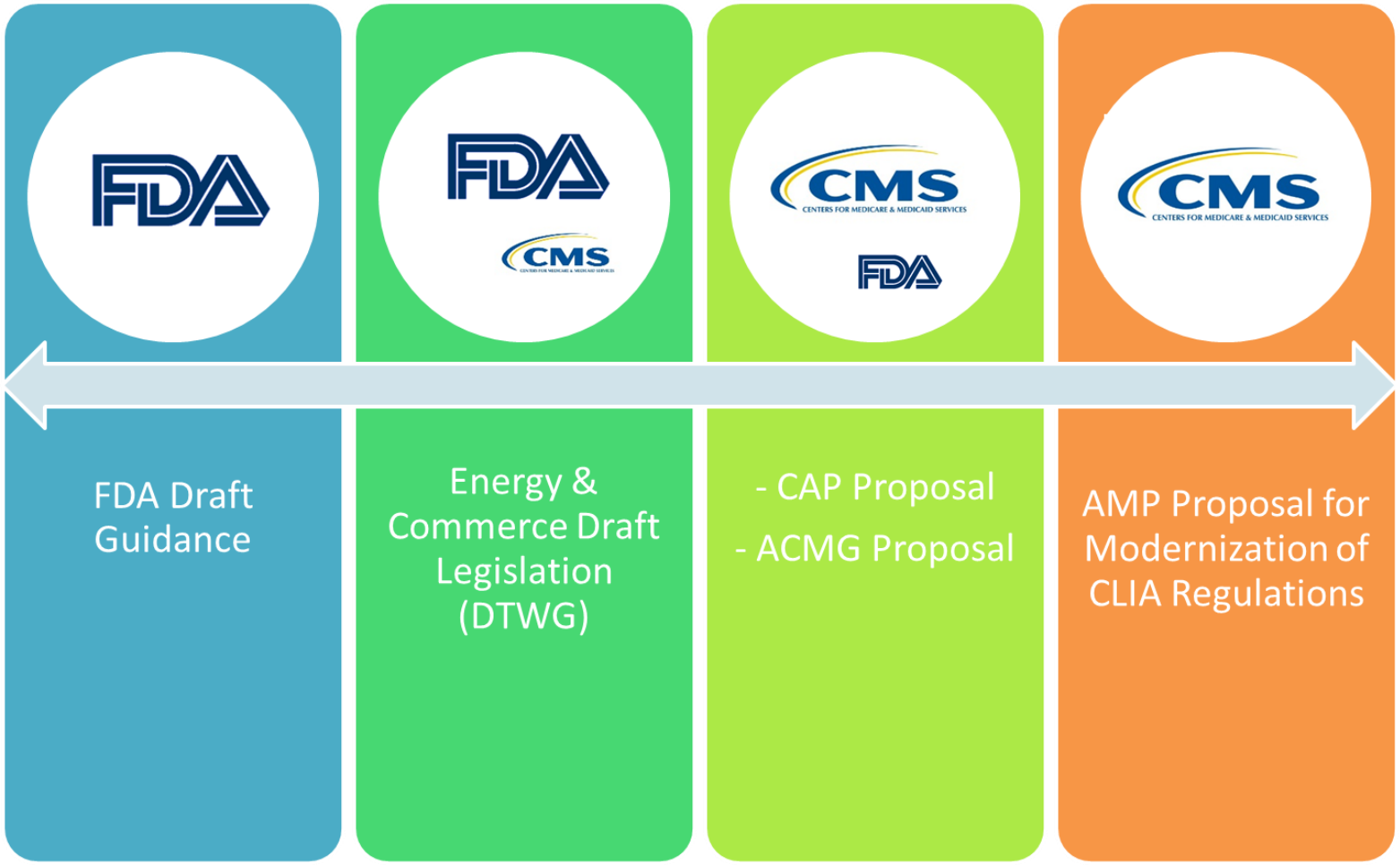
History of LDT Regulation

- The 1976 Medical Device Amendments to the Federal Food, Drug, and Cosmetic Act (FD&CA) authorized the FDA to regulate medical devices such as *in vitro* diagnostic devices (IVDs)
  - Safety, efficacy, intended use, manufacturing
- Laboratory developed tests (LDTs) are regulated under the 1988 Clinical Laboratory Improvement Amendments (CLIA)
  - Enables clinical laboratories to modify IVDs and develop their own tests
  - Validation to ensure tests meet performance standards
- In 2014, the FDA announced its intention to begin regulating all LDTs as medical devices.

Proposals for Regulating LDTs



FDA Framework for Regulatory Oversight of LDTs

- Draft Guidances released in Fall 2014 to regulate all LDTs
  - LDTs will be subject to premarket review requirements like IVDs
- Oversight will be phased in over a 9 year period, first for high risk LDTs, followed by moderate risk LDTs
  - Low risk LDTs will not require premarket review
- Regulatory carve outs for "traditional LDTs", LDTs for rare diseases, and LDTs for unmet medical needs
- FDA staff have indicated intent to release final guidance by end of this year

House Energy and Commerce Discussion Drafts

- Adapted from a 2015 proposal from the Diagnostic Test Working Group (DTWG), a consortium of mostly commercial laboratories and IVD manufacturers.
- LDTs and IVDs regulated identically via a risk based approach under a new center at the FDA.
- Tests undergo premarket review by the FDA, and then fall under a strengthened CLIA would oversee laboratory operations.
- Special pathways for tests for rare diseases, emergency use, and unmet needs
- Grandfathering provision for current tests

CLIA Modernization Proposals

- Proposals (ACMG, AMP, and others) based primarily on strengthening CLIA oversight
- While details differ in each proposal, each proposal:
  - Establishes standards for clinical validity and strengthen established standards related to quality control, quality assurance, personnel standards, and regular proficiency testing.
  - Preserves patient access to care
  - Ensures quality of high complexity testing services and procedures based on risk
  - Streamlined, cost-effective approach
  - Limited, well-defined role for FDA

The Current State of Play

- FDA Final Guidance
  - Is the most likely of the three alternatives
  - Final guidance is under review within the Federal Government, and release could be imminent
- House E&C proposal
  - House E&C has released 2 discussion drafts subject to significant stakeholder concerns
  - A third draft is under development but unclear if and when it will be marked up for consideration
- CLIA-based proposals
  - Senate HELP said to be working on an oversight proposal that may include a CLIA modernization approach
  - September 20 HELP Hearing

Questions?

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