The Squeeze on Molecular Pathology

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AMP Economic Affairs Committee, past-Chair

CAP Economic Affairs Committee, member

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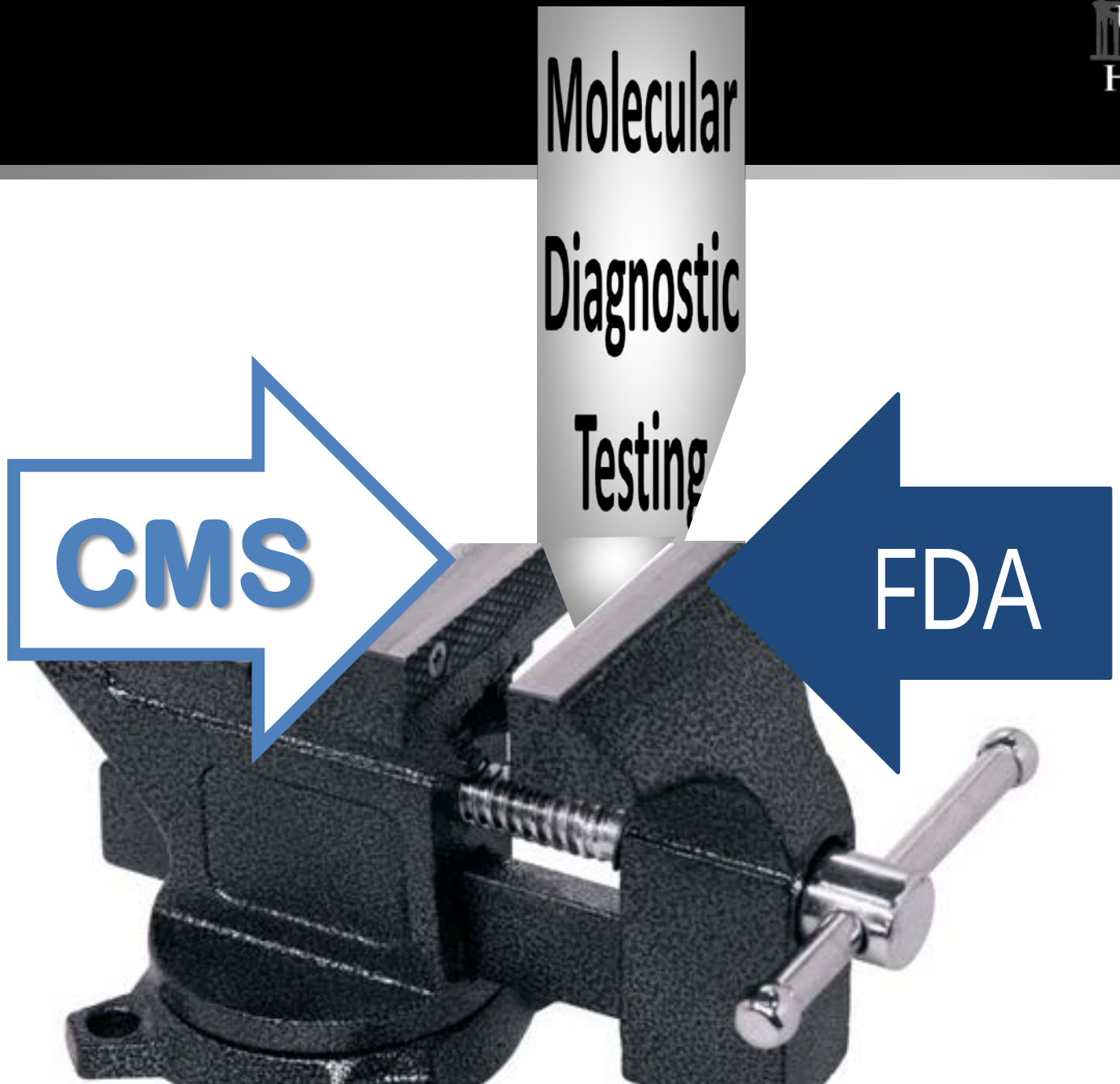
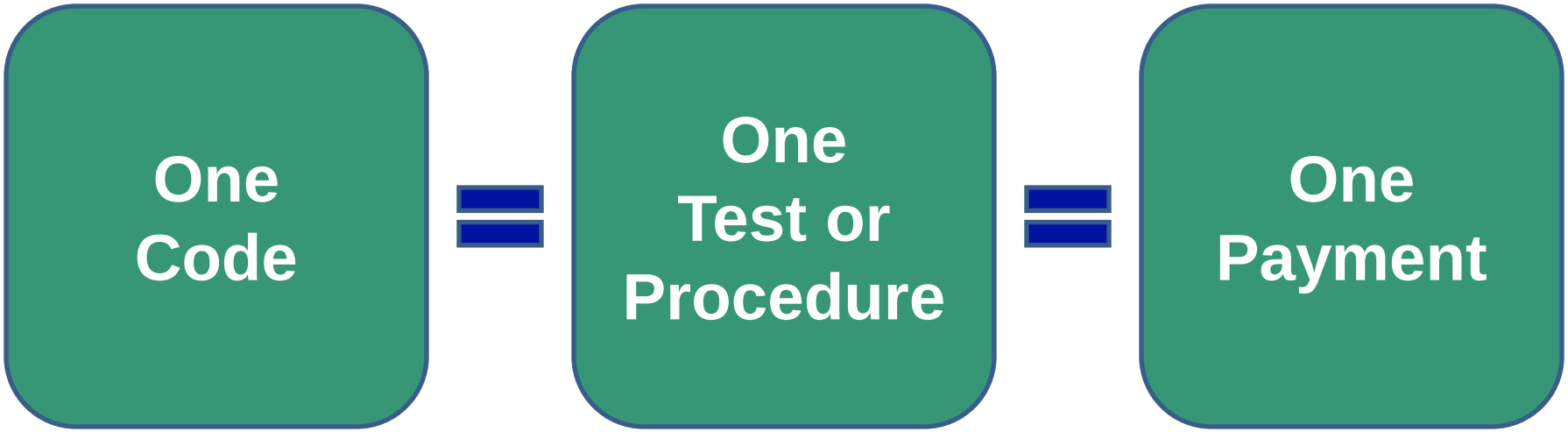
Pathology Coding Caucus, AMP representative


Molecular
Diagnostic
Testing
CMS
FDA

Original Molecular Method "Stacking" CPT codes

- 83890 Nucleic acid, isolation or extraction, EACH type 5.68
- 83891 extraction, highly purified nucleic acid, EACH type 5.68
- 83892 enzymatic digestion, EACH treatment 5.68
- 83893 dot/slot blot production, EACH preparation 5.68
- 83894 nucleic acid separation – electrophoresis, EACH 5.68
- 83896 nucleic acid probe, EACH 5.68
- 83897 nucleic acid transfer (e.g. Southern blot), EACH 5.68
- 83898 amplification (e.g. PCR), EACH 23.74
- 83900 amplification, multiplex, 1st 2 targets 47.48
- 83901 amplification, multiplex, EACH additional target 23.74
- 83902 'reverse transcription Codes' 20.11
- 83903 mutation scanning, physical properties, EACH 23.74
- 83904 mutation ID, sequencing, EACH 23.74
- 83905 mutation ID, allele specific transcription 23.74
- 83906 mutation ID, allele specific translation 23.74
- 83907 cell lysis prior to extraction (stool/paraffin), EACH 18.92
- 83908 signal amplification, EACH sequence 23.74
- 83909 nucleic acid separation–high res, EACH 23.74
- 83912 (C/P) interpretation and report 5.68/18.81
- 83913 RNA stabilization 18.92
- 83914 mutation ID, ligation/extension, EACH segment 23.74

Unit of Service



Evolution of the Molecular and Genomic Procedure Codes

University of Iowa Health Care

2009
- AMP Economic Affairs Committee drafts coding reform proposal

2010
- AMA Ad Hoc Molecular Pathology Workgroup develops structure through a few face to face meetings and weekly conference calls

2011
- Coding Change Proposals submitted for the next 12 tri-annual cycles

2012
- First Tier 1 and Tier 2 codes published in CPT
- Placement of codes on CLFS in November and initiation of gap filling

2013
- AMP genomic sequence procedures (GSP) draft proposal to AMA
- 21 AMA workgroup descriptors developed and accepted

2014
- CPT Editorial Panel accepts first GSPs for Jan 1, 2015 effective date

Molecular Pathology Procedures

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Tier 1:

Individual analyte codes for higher volume tests	>120 codes

Tier 2:

Complexity-based codes, less common tests	9 codes of >600 analytes

MAAA:

Multi-analyte assays using algorithm analysis	~2 dozen codes

GSP:

Genomic sequencing procedures	~2 dozen codes

CMS Pricing Procedures

University of Iowa Health Care

Crosswalk

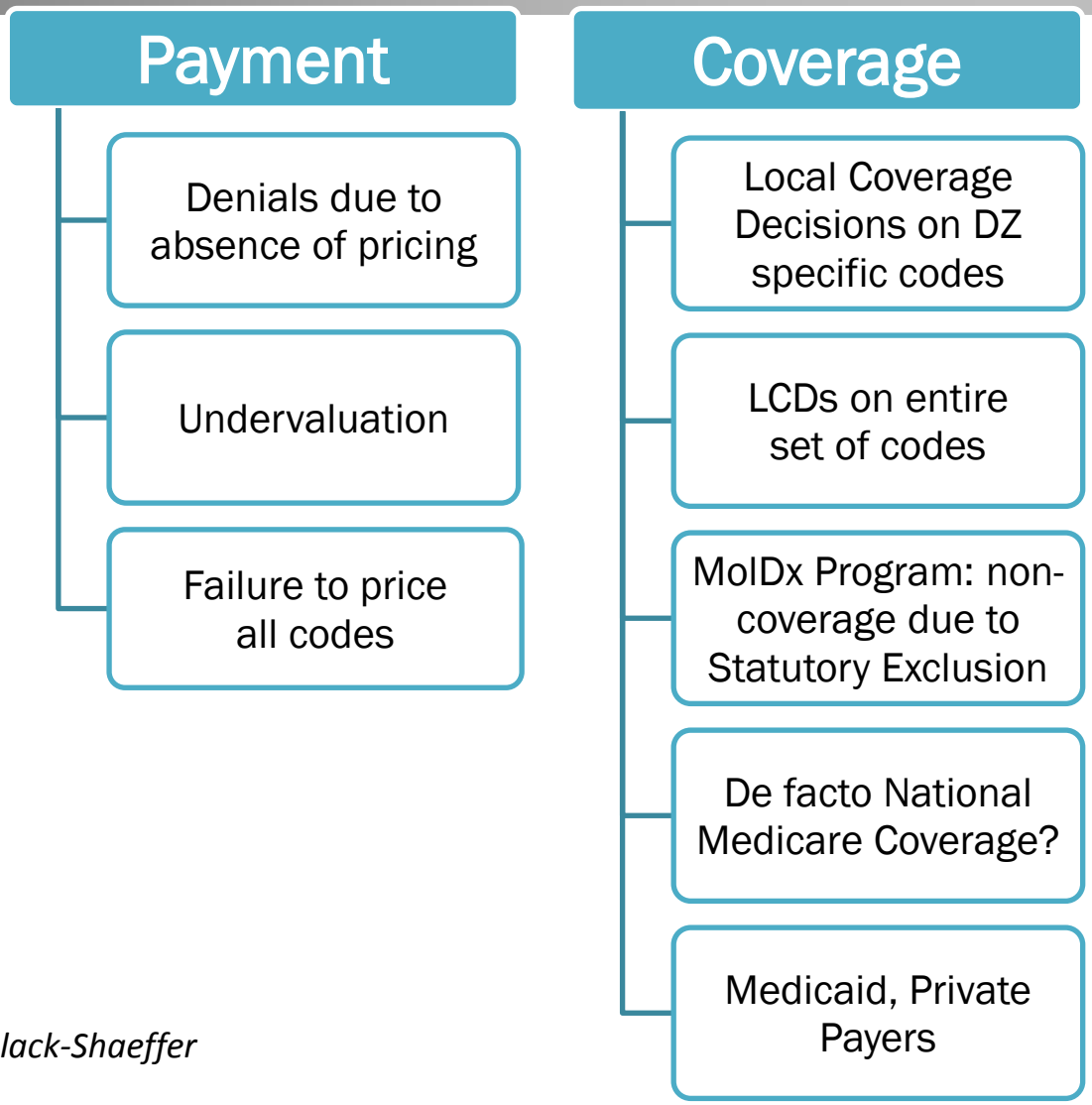
VS.

Gap Fill

Stakeholders make recommendations to CMS for crosswalking values of existing codes to new codes

Medicare Administrative Contractors (MACs) determine prices for CMS to take median value

Consequences of Gap Fill



Modified from Stephen Black-Shaeffer and CAP

Response Comments to Draft Local Coverage Determinations

dLCD No.	LCD	MAC	Due Date	Duplicates
	Molecular Diagnostic Tests	Noridian	March 30, 2015	
	MolDx: Comprehensive Genomic Profiling for Non-Small Cell Lung Cancer	Palmetto	March 27, 2015	
	Biomarkers Overview	Novitas	March 19, 2015	
	Infectious Disease Molecular Diagnostic Testing	CGS	March 30, 2015	
	Molecular RBC Phenotyping (DL35827)	Palmetto	March 27, 2015	
	Genetic Testing for Hypercoagulability / Thrombophilia	Palmetto	March 27, 2015	
DL36055	In Vitro Chemosensitivity and Chemoresistance Assays	Novitas	July 9, 2015	
DL35006	Controlled Substance Monitoring and Drugs of Abuse Testing	Novitas	July 9, 2015	L35105
DL34864	Loss-of-Heterozygosity Based Topographic Genotyping with PathfinderTG	Novitas	July 9, 2015	
DL35974	MGMT Promoter Methylation Analysis	Palmetto	July 24, 2015	DL36113
DL36125	MolDx: Prosigna Breast Cancer Assay	Palmetto	July 24, 2015	DL36127
DL36044	MolDX: Genetic Testing for BCR-ABL Negative Myeloproliferative Disease	Palmetto	July 24, 2015	DL36117, DL36098
DL36082	MolDX: BRCA1 and BRCA2 Genetic Testing	Palmetto	July 24, 2015	DL36115
DL36033	MolDX: HLA-B15:02 Genetic Testing	Palmetto	July 24, 2015	
DL36115	MoPath: BRCA1 and BRCA2 Genetic Testing	CGS	August 3, 2015	DL36082
DL36127	MoPath: Breast Cancer Assay: Prosigna	CGS	August 3, 2015	DL36125
DL36004	MoPath: Breast Cancer Index Genetic Assay	CGS	August 3, 2015	DL36125
DL36009	MoPath: Decipher Prostate Cancer Classifier Assay	CGS	August 3, 2015	
DL36117	MoPath: Genetic Testing for BCR-ABL Negative Myeloproliferative Disease	CGS	August 3, 2015	DL36044, DL36098
DL36002	MoPath: Prolaris Prostate Cancer Genomic Assay	CGS	August 3, 2015	
DL36011	NDD United is an alliance of 2,500 national, state, and local organizations workir	CGS	August 3, 2015	
DL36113	MoPath: MGMT Promotor Methylation Analysis	CGS	August 3, 2015	DL35974
DL35986	Special Histochemical Stains and Immunohistochemical Stains	CGS	August 3, 2015	
DL35984	MoPath: Genetic Testing for Hypercoagulability/Thrombophilia	CGS	August 3, 2015	Comments previously drafted
DL36006	MoPath: ConfirmMDx Epigenetic Molecular Assay	CGS	August 3, 2015	
DL36194	NSCLC, Comprehensive Genomic Profile Testing	Noridian	August 10, 2015	
DL36004	MoPath: Breast Cancer Index Genetic Assay	CGS	August 3, 2015	
DL36139	MoPath: Biomarkers in Cardiovascular Risk Assessment	CGS	August 3, 2015	DL36129
DL36153	MolDX: Genomic Health Oncotype DX Prostate Cancer Assay	Palmetto	July 24, 2015	

2013 Gap Fill Results

HCPCS	Descriptor	NLA
81206	BCR/ABL	$225
81210	BRAF	$180
81220	CFTR	No value
81225	CYP2C19	$294
81235	EGFR	$332
81241	FV	$84
81275	KRAS	$198

What To Do About NGS Procedures?

- First 21 Genomic Sequencing Procedures approved last year for implementation in 2015
- AMP and CAP submitted crosswalk recommendations at the 2014 CLFS Public Meeting
- Ultimately CMS chose to gap fill
- AMP performed a Cost and Value Analysis of representative GSPs

AMP EAC Cost and Value Project

- Microcosting and health economic modeling of
  - Tumor, 5-50 genes
  - Hearing loss
  - Exome
- 13 protocols from 9 clinical laboratories
- Tynan Consulting & Boston Healthcare Associates collected and organized the data

BioReference LABORATORIES

BD BD Biosciences

Roche

Agilent Technologies

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Detailed Micro-Costing Model

Individual Protocol Steps

Supplies/ Consumables

Reagent/ Equipment List

Personnel Time/Cost

Assay Section		Reagents and Disposables (Consumables)						Equipment					Personnel			
	Steps	Consumables	Consumable Cost	Qty	Unit	Batch Size	Cost per Step	Equipment Used	Equipment Cost	Equipment Time (min)	Quantity	Cost per Step	Personnel Type	Hands On Personnel Time (min)	Personnel Cost Per Min	Cost per Step
DNA Extraction	lood or tumor)															
	lity of each DNA sample relative to be made by dilution.															
	idization of strand specific leotide primed extension and															
	nding on platform. Some the Agilent SureSelect, Roche's n and Fluidigm's Access Array.						$ -					$ -				$ -
	e barcodes to samples. Paramagnetic beads are used for cleanup prior to quantification.						$ -					$ -				$ -
Library Quantification & Normalization	Assessment of the quality and quantity of each library. Libraries are normalized by appropriate dilution.						$ -					$ -				$ -
Library Denaturing & Pooling	Libraries are combined into a single pool and denatured.						$ -					$ -				$ -
Sequence Generation	Sequencing performed by Ion Torrent, MiSeq, HiSeq, etc.						$ -					$ -				$ -
Documentation	Recording run metrics						$ -					$ -				$ -
Initial Data Review/Quality Assessment	Review of FAST-Q or BAM file data to ensure correct reads have been made and it is ready for further analysis using pipeline software						$ -					$ -				$ -
Bioinformatics Pipeline Analysis	Analysis of file using bioinformatics software						$ -					$ -				$ -
	Computer support for software						$ -					$ -				$ -
Bioinformatics Output Initial Review	Analysis of output of bioinformatics pipeline using data visualization software						$ -					$ -				$ -
Assay Gap-filling Testing	Sanger Sequencing						$ -					$ -				$ -
Confirmatory Testing	Sanger Sequencing						$ -					$ -				$ -
Report Generation & Sign Out	Comparison of data to reference gene databases						$ -					$ -				$ -
	Generation of draft report						$ -					$ -				$ -
	Review/QC/sign-out of report						$ -					$ -				$ -
Data Storage	Long term/Short-term Data Storage of data on computers, back-up systems						$ -					$ -				$ -
Validation	Time/effort to validate the assay (see software and upkeep tab)						$ -					$ -				$ -
Maintenance	On-going upkeep of analyzer and software systems						$ -					$ -				$ -
		Overal Total														
	Totals Per Section without VMO	$ -					$ -					$ -				$ -
	Total Per Sample without VMO	#DIV/0!					#DIV/0!					#DIV/0!				#DIV/0!

AMP ASSOCIATION FOR MOLECULAR PATHOLOGY

Microcost Findings

- Cost analysis results:

  81445 (tumor, 5-50 genes): $578 - $908

  81430 (hearing loss): $1898 - $1949

  81415 (exome): $1499 - $3388

- Key cost drivers were:
  - Kit reagents, equipment, reporting, personnel time
  - The greater the number of specimens in the run the lesser the overall costs (up to the batch size)
- Significant variation in validation and assay development expenses from first version to later versions
- Group reviews cost significantly more than reviews done mainly by pipeline

Health Economic Modeling

Objective

Estimate and compare the cost-utility of genomic sequencing procedures with that of standard testing and medical intervention

Design Principles

1) Payer cost Impact Modeling:
   - Avoidance of costs
     (eg procedures, visits, imaging, side effects, adverse events)
2) Transparency
3) Flexibility to change inputs

HE Modeling Steps

1) Define current diagnostic and treatment pathways
   - Literature review
   - KOL consultation
2) Develop and program US Payer-oriented Cost Impact Model

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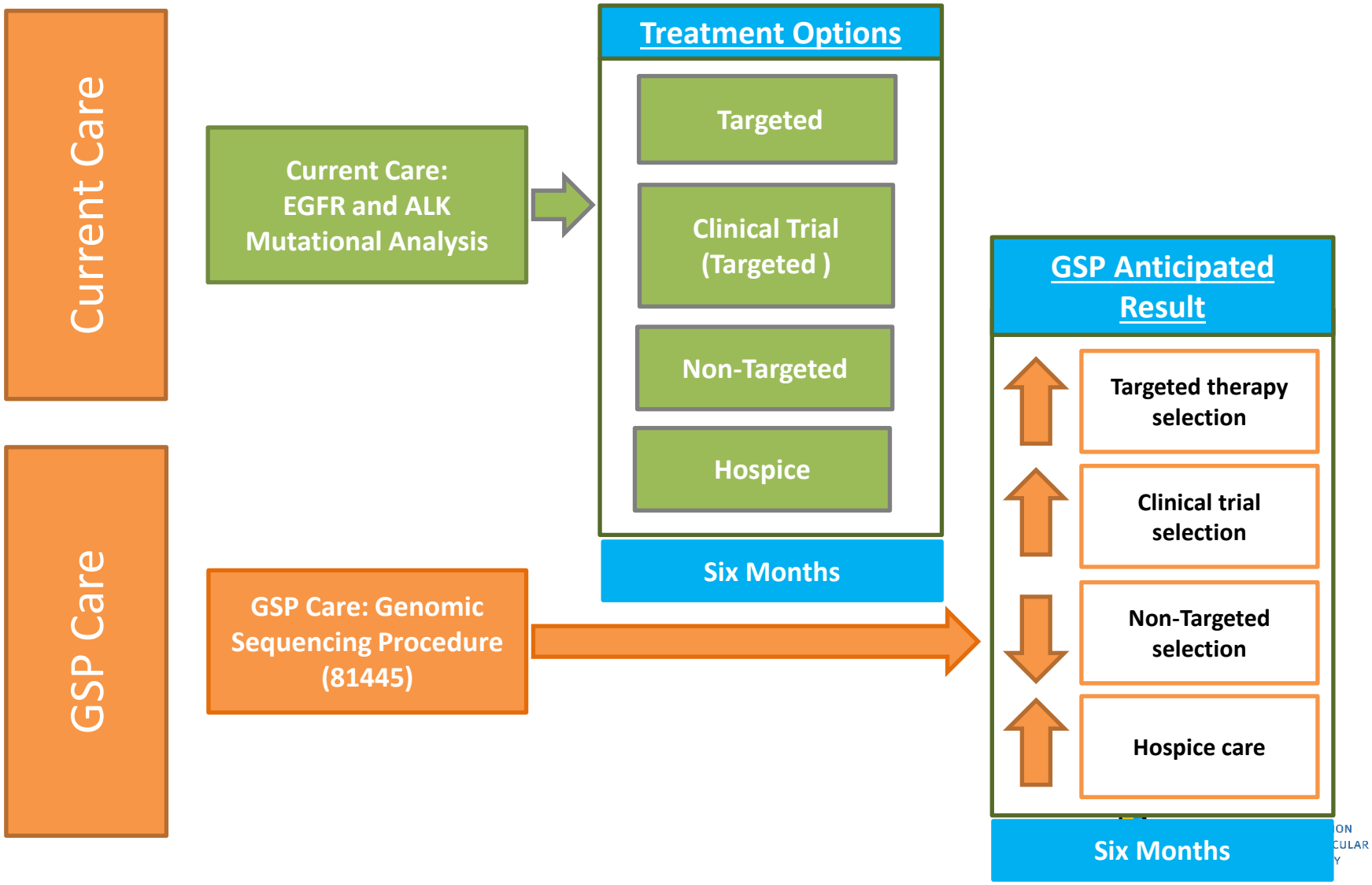
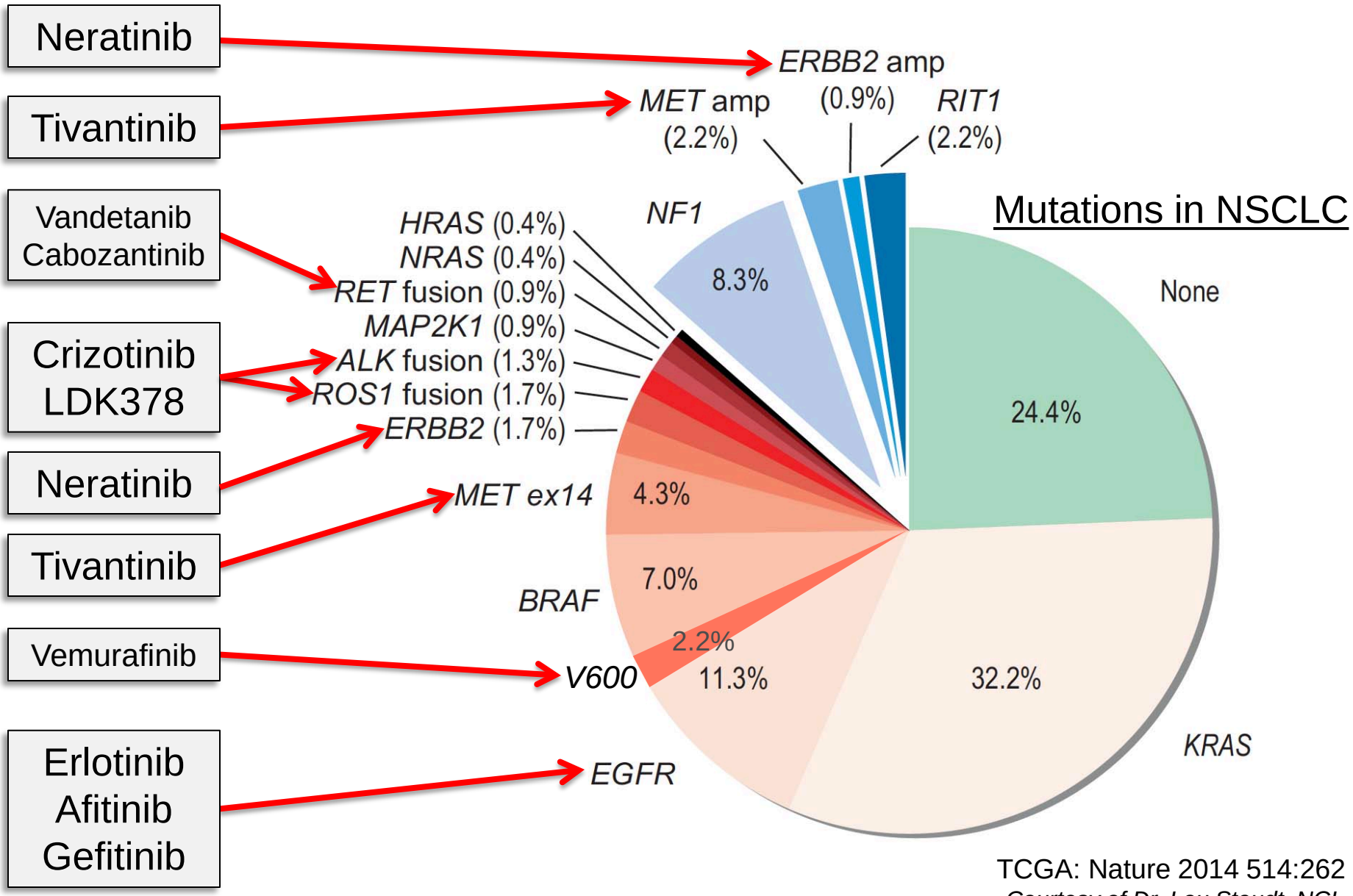
Model Framework: NSCLC



GSP Care: Additive Driver Genes to EGFR and ALK



TCGA: Nature 2014 514:262

Courtesy of Dr. Lou Staudt, NCI

NSCLC Inputs and Impact of GSP

Variable	Input	Impact	Sources
Plan Demographics			
# of covered lives	1 million		Representative plan size
Lung cancer incidence	.07%		2014 NCI SEER data & U.S. Census
Diagnoses at stage IIB-IV	88.2%		Wisnivesky et al. Chest 2005, NCI SEER Stat Fact Sheet 2014
# diagnosed with advanced or metastatic cancer	5,496		Based on plan covered lives, lung cancer incidence rate & percent diagnoses at stage IIIB/IV
Standard of Care			
Treatment Decisions: Targeted therapy Non-targeted therapy Clinical trial Hospice care	 6% 83% 4% 7%	 13% (↑) 20% (↓) 54% (↑) 27% (↑)	The Cancer Genome Research Network 2014; Pan et al. 2013; NCI Cancer Bulletin 2014; Mattson Jack Treatment Architecture 2007
# adverse events in patients receiving treatment	207	137 (↓)	Adverse event rates for pharmacologic treatments weighted by treatment utilization percentage
Total treatment cost	$10.2M	$7.5M (↓)	Weighted average of individual treatment decision pathways from published data and KOLs
Total cost of genetic testing		↑ $0.13M	Medicare Fee Schedule 2014, EGFR+ALK $467, GSP$700

EAC NGS Value Models

- Hearing loss demonstrated a $1.5M to $2.5M care cost savings
- Pediatric neurodevelopmental disorders (exome)
  - At average test cost resulted in $.9 to $1.3M savings
  - Lowest test cost – $10 savings
  - Most expensive test – $8-10M increase in care costs.
- Value discussion needs to be continued with payers

EAC NGS Value Models

- AMP released the models in March 2015
  - https://www.amp.org/committees/economics/NGSPricingProject.cfm
- Almost 400 downloads of the on-line materials
  - Survey of those
    - Microcosting template was very useful
    - Majority used the AMP template to cost their own assays
    - Costs were similar to AMP results
    - A few communicated this information to their MAC

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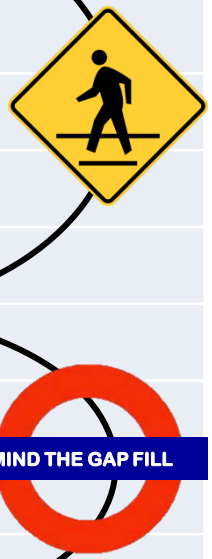
CMS 2016 Pricing Determinations

HCPCS	Short name	National Limitation Amount
81161	DMD/BMD	$ 140.00
81246	FLT3 TKD variants	$ 82.96
81287	MGMT	$ 83.01
81288	MLH1 promoter methylation	$ 159.48
81313	PCA/KLK3	$ 260.00
81435	Hereditary colon cancer	$ 795.95
81436	Hereditary colon cancer (dup/del)	$ 795.95
81445	Solid organ neoplasm (5-50 genes)	$ 597.31
81450	Hematolymphoid neoplasm (5-50 genes)	$ 647.75



PAMA Legislation: HR 4302

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2014

- New tests for which new payment method applies are those for which a new or revised HCPS code is issued after 4/1/14
- **Payment for new laboratory tests subject to current cross-walking and gap-filling processes thru 2016**

2015

- *By 1/1/15:* MACs required to abide by existing (LCD) process
- *August:* Expert advisory panel assembled for first meeting
- *September:* issued rules on parameters for data collection

2016

- "Applicable laboratories" must report to CMS certain private market data related to payment rates and test volume. Most hospitals will be excluded. $10,000 penalty

2017

- *Beginning 1/1/17:* Prices based on "weighted median" prices of private market data will become new payment rates

2018-19

- Reductions in payment to laboratories for a given test may not exceed 10% per year

FDA 2014 DRAFT GUIDANCE FRAMEWORK FOR REGULATORY OVERSIGHT OF LABORATORY DEVELOPED TESTS

http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

University of Iowa Hospitals and Clinics

- 730 beds
- ~32,000 in-patient hospital admissions annually
- Tertiary care center for Iowa
- NCI-designated Comprehensive Cancer Center
- >200 outpatient clinics and ~914,300 clinic visits in 2014

Molecular Pathology Tests

Molecular Oncology

1. AML and MDS 30 gene Panel
2. BCR-ABL, t(9;22), RNA Quantitation
3. BRAF Mutation Detection by Sequencing
4. BRAF V600E mutation detection by primer extension
5. Calreticulin
6. Cancer Mutation Profiling 50 Gene Panel
7. CEBPA Mutation Detection by Sequencing
8. EGFR Mutation Detection by Sequencing
9. FLT3 Mutation Detection
10. HRAS Mutation Analysis
11. IDH1 & IDH2 Mutation Detection by Sequencing
12. IgH Rearrangement (B cell clonality) by PCR
13. JAK2 V617F Mutation Detection Assay
14. KIT Mutation Detection by Sequencing
15. KRAS Mutation Detection by Sequencing
16. Microsatellite Instability testing
17. NPM1 Mutation Detection
18. NRAS Mutation Detection by Sequencing
19. Pan-Sarcoma related Fusion Detection
20. PDGFRA Mutation Detection by Sequencing
21. Quantitative JAK2 V617F Mutation Detection
22. TCR gamma Rearrangement(T cell clonality) by PCR

Molecular Genetics

1. Angelman syndrome
2. Factor V-Leiden/Factor II Gene PCR Assay
3. Fragile X, DNA Testing
4. Hemochromatosis, DNA Testing
5. Huntington disease, DNA testing
6. Identity Testing
7. Prader-Willi syndrome
8. Calpain 3 (CAPN3) sequencing
9. Dysferlin (DYSF)gene sequence analysis
10. Dystroglycanopathy Mutation Profiling 21 Gene Panel
11. Fascioscapulohumeral dystrophy (FSHD1)
12. FKRP Gene Sequencing
13. FSHD 4qA/4qB haplotyping
14. FSHD, prenatal
15. FSHD2 Hypomethylation
16. Fukutin CongenitalMuscular Dystrophy (FCMD) Japanese Founder Mutation
17. Fukutin gene sequencing
18. ISPD gene sequencing
19. Lamin A/C Gene Sequencing
20. LARGE Gene Sequencing
21. LGMD Autosomal Recessive (LGPCR) Mutation Analysis
22. Myotonic Dystrophy (DM1) Type 1 DNA testing
23. POMGNT1 Sequencing
24. POMT1 Sequencing
25. POMT2 Sequencing
26. SMCHD1 Gene Sequencing
27. Transforming Growth Factor Beta Receptor 2 (exon 5, R460C)

FDA Draft Guidance

- Risk-based (high, moderate and low)
- Phased-in (9 years)
- Carve outs:
  - Rare Dx, unmet needs, traditional LDTs, HLA, etc
- Notification and Medical Device Reporting (MDR)
  - of adverse events

FDA Notification

- Within 6 months of final publication
- Requirements:
  1. test name
  2. monthly volume
  3. intended use
  4. clinical use
  5. analyte
  6. disease/condition
  7. patient population (whether it includes pediatrics)
  8. sample type
  9. method
  10. If test is a modified FDA approved test what are the modifications

Risk Based Approach

- Class III: most complex, highest risk
  - Premarket Application [PMA]
  - Safe and effective
- Class II: less complex, moderate risk
  - Premarket Notification [510(k)]
  - Substantial equivalence, special controls
- Class I: common, low risk devices
  - Most exempt from premarket submission
  - General controls

Section 513(a)(1) of the FD&C Act (21 U.S.C. 360c(a)(1)).

High Risk Devices

- For high and moderate risk LDTs, FDA intends to enforce regulatory requirements, including registration and listing, adverse event reporting, premarket review, and quality system requirements, after guidance is finalized as follows:
  - *High-risk LDTs:*
    - Registration and listing and adverse event reporting begin @ 6 months
    - Premarket review requirements begin @ 12 months
    - Phase-in over 4 years for the remaining high-risk devices
    - Devices would remain on the market during review and
    - FDA's consideration of applications is in this order
      a. LDTs with the same intended use as a cleared or approved companion diagnostic
      b. LDTs with the same intended use as an FDA-approved Class III medical device
      c. Certain LDTs for determining the safety or efficacy of blood or blood products

What Does This Mean For Labs?

- Not sure what the costs will be
- Not sure of the paperwork requirements
- Not sure of timeframe of approvals

Responses to Draft Guidance

Proponents

- Need assurances of analytical validity, clinical validity, and clinical utility
- No transparency in claims or validity
- Don't know what labs are doing
- Need MDR

Opponents

- Clinical Laboratory Improvement Amendments (CLIA) of 1988
  - provide sufficient legal authority for CMS to address public health issues with laboratory testing through the CLIA program
  - requires documented analytical validation
  - monitors performance
- All tests already registered with CLIA
- MDR not granular enough; CLIA requires ongoing QA
- Carve outs are subjective
- Time and Expense of regulatory submissions

FDA 20 "Case Studies"

- Claim these support the Agency's move to regulate laboratory developed procedures
- Examples for lyme testing, HPV testing, ovarian cancer (OvaCheck, OvaSure, PreOvar), terminal cancer (TargetNow), Oncotype Dx Breast, NIPT (neonatal trisomy in maternal CFD), BRAF, etc
- Cite issues with false positive or false negative rates, insufficient clinical validation, failure to appropriately interpret results and others

http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UCM472777.pdf

Facts FDA Ignored: An analysis of the FDA report by the AMP

- "…mostly a hodgepodge of outlier assays including tests that were never offered, tests for which comparable FDA assays perform poorly, tests for poorly defined disorders with psychologic components, and use of an FDA-approved test off-label."
- Concluded that only a few of the 20 tests identified by the FDA could cause patient harms that FDA oversight might have prevented

http://www.amp.org/emailads/AMPPressRelease121615.html

LDTs or LDPs

- How do you know they are any good?
  - CLIA?
  - FDA?
- Who has regulatory responsibility for overseeing LDTs?

FDA's Role

- Oversees medical devices, not medical practice
- Assures safety and effectiveness
  - Very limited clinical validity; clinical utility – not at all
- Reactive: can only evaluate products brought before it for specific indications
  - Black box mentality: can't make any judgments about red boxes or blue boxes
  - Slow, deliberate process

CLIA's Role

http://wwwn.cdc.gov/CLIA/

- Ensures performance through ongoing quality process, proficiency testing, and biennial laboratory inspection
- Requires trained certified professionals as directors of clinical laboratories
- Imposes clinical consultation requirements on directors (or designee) for appropriate selection of tests and interpretation for specific patient use (i.e. clinical validity and clinical utility)
- Director responsible for quality and safety; which includes analytical and clinical validity

Diagnostic Test Working Group (DTWG) Proposal

- Separate into
  - Test Development
  - Laboratory Operations
  - Medical Practice
- Defines new category of “In Vitro Clinical Test”
  - Includes both finished test product and LDPs
  - Not regulated as devices, drugs or biologics
  - Creates a new FDA Center to regulate
- Risk-based classification

DTWG Proposal (cont'd)

- Laboratory developed tests can/should be regulated similarly to distributed tests
- Recognizes that laboratories perform some functions that distributed manufacturers do not
- Recognizes the need for all laboratory developed tests to be clinically validated
- Uses existing FDA approval mechanism

AMP Proposal for CLIA Program Modernization

- Desired Outcomes:
  - Patients receive the most appropriate test(s) for their condition
  - Laboratory tests should be accurate and reliable
  - Health care professionals are able to provide professional services and practice medicine without undue restrictions
  - Regulatory oversight does not slow innovation,
    - constrain flexibility and adaptability, or limit a test's sustainability as a result of being unduly burdensome and overly expensive

http://www.amp.org/advocacy/CLIAModernization.cfm

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AMP Proposal for CLIA Program Modernization

- LDPs
  - are **not medical devices**
  - **are distinct** from boxed and shipped laboratory test kits
  - are a component of professional laboratory practice
- Regulation of professional practice should be **by relevant licensure and credentialing bodies**
- Laboratory professionals **promote patient safety through** the use of **professional judgment at every stage** of the LDP process
- Any new regulatory framework **should not be duplicative** of existing regulations
- Any proposed regulation **should not shift product liability** from manufacturers to medical professionals or their laboratories

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CLIA Program Modernization

Enhance transparency

Ensure quality

Preserve innovation

Submission and Publication Process

Laboratories will have to…

- Adopt the standardized format
- Submit the LDP information to CMS/Third Party Reviewer
  - Must be submitted before the LDP is introduced into clinical service:
    - High risk: 90 days
    - Moderate risk: 30 days
    - Moderate risk LDPs introduced prior to 4/24/2003 exempt from publication & review requirements
    - Low risk: Exempt

Additional Components

- LDP Submission Review Requirements by CMS including development of an Advisory Board of subject matter experts
  - Excludes any entity that sets payment or coverage policy
- Must include necessary data to ensure clinical validity
- Risk stratification has proprietary assays as highest risk
- Exemptions for public health surveillance, LDPs already approved by a state that has exempt status under CLIA regs (ie NYS approval), and compassionate use

CLIA Modernization Proposal Summary

- Tiered; risk-based
- Regulates LDPs as professional services
- Assures both analytical and clinical validity without jeopardizing innovation
- Provides transparency so physicians and patients have essential information
- Levels the playing field by applying the same regulatory principles to anyone who develops an LDP
- Provides for pre-introduction review of high & moderate risk LDPs
- Requires proficiency testing or alternative assessment for all LDPs
- Does not change states' exempt status under CLIA
- Avoids duplication of activities within and between federal agencies

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Conclusions

- Issues of coding, pricing, coverage and reimbursement will continue – time and evidence will improve outcomes
- Unclear whether FDA LDT guidance will be adopted
  - Anticipate approval process will be costly, duplicative, and still may not ensure patient safety
- AMP proposal is sensible, ensures patient safety, acknowledges the responsibility of laboratory professionals
- Involvement of subject matter experts including laboratory professionals is critical
- Labs should be planning ahead

2015 Committee Members

Economic Affairs Committee Members:

- Aaron D. Bossler, MD, PhD, Chair
- Samuel Caughron, MD, Vice-Chair
- Jill Hagenkord, MD – New codes VC
- Richard Press, MD, PhD – Coverage VC
- Dara Aisner, MD, PhD
- Pranil Chandra, DO
- Roger Klein, MD, PhD, JD *ex officio* PRC
- Nina Longtine, MD, PhD
- Elaine Lyon, PhD
- Linda Sabatini, PhD
- Michele Schoonmaker, PhD
- Ester Stein, MBA
- Katherine Tynan, PhD
- Jan Nowak, MD, PhD, Advisor
- Tara Burke, PhD AMP support staff
- Mary Williams, PhD, AMP CEO

NGS Pricing Project Oversight Committee:

- Linda Sabatini, PhD, Sub-committee Chair (EAC)
- Aaron D. Bossler MD, PhD (EAC)
- Janina Longtine, MD (AMP Board)
- Jill Hagenkord, MD (EAC)
- Madhuri Hegde, PhD (AMP Board)
- Ester Stein (EAC)
- Vivianna Van Deerlin, MD, PhD (AMP Board)
- Katherine Tynan, PhD, Project Manager

Consultants

- Erika Miller, JD CRD Associates
- Zara Day, JD CRD Associates
- Charles Mathews Boston Healthcare

Thank You

CMS HCPCS Code

- G0452 Molecular diagnostics; interpretation and report
  - Section §415.130(b)(4) of the regulations and section 60 of the Claims Processing Manual (IOM 100-04, Ch. 12, section 60.E.) specify certain requirements for billing the professional component of certain clinical laboratory services including that the interpretation
    - (1) must be requested by the patient's attending physician,
      - We note that a hospital's standing order policy can be used as a substitute for the individual request by a patient's attending physician.
    - (2) must result in a written narrative report included in the patient's medical record, and
    - (3) requires the exercise of medical judgment by the consultant physician.
  - RVU = 0.37

Hearing Loss

- For a plan size of 1 million members, a
- Cost savings of $2.36 million and an increase in diagnostic yield from 25% to 36%, was demonstrated upon incorporation of GSPs into the diagnostic approach, using an average cost of $1,499, as per our microcosting analysis. The diagnostic yield of hearing loss GSP was assumed to be 20%. We also used the minimum and maximum cost of hearing loss GSP from our microcosting analysis in the budget-impact model. At a GSP cost of $1048 (minimum), the cost-savings from diagnostic work-up increased to $3.16 million and at a GSP cost of $1,949 (maximum), the cost-savings reduced to $1.57 million.

FDA LDT Definition

- “an in vitro diagnostic that is intended for clinical use and designed, manufactured and used within a single lab.”
  - "**device**" means an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is--
    1. recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them,
    2. **intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man** or other animals, or
    3. intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes.
- A procedure developed by a laboratory to fulfill a clinical need

Safe and Effective

- Examination of interventions in the processes by which various phenomena affect health and disease.
- Neither these phenomena (whether they be biological, psychological, or social) nor the interventions (often, technologies) need be thought of as having a fully predictable mechanistic effect.
- A probabilistic view, that is, when an event occurs, there is a range of possibilities that other events will occur, is a more useful approach.
- The concept of probability is used to summarize the effects of causal variables which are unknown or not taken into account.
- Thus, we can speak of estimating or evaluating efficacy and safety, but not exactly determining them.
- Specific technologies have certain probabilities of effects; therefore, efficacy and safety information is normally expressed in terms of probabilities.

https://www.princeton.edu/~ota/disk3/1978/7805/780504.PDF

Analytical Verification and Validation

Accuracy	Method Comparison(s)
	Specimen Types
	Matrix Comparison(s)
Analytical Sensitivity	Limit of Blank
	Limit of Detection
	Limits of Quantitation (Upper and Lower)
	Linearity and Reportable Range
	Minimum Input Quantity and Quality
	Minimum Tumor Content
Analytical Specificity	Primer and Probe Specificity
	Interfering Substances
Precision	Repeatability (i.e., “intra-run”, within run)
	Intermediate Precision (i.e., “inter-run”, between runs, “intralab”, within lab)
	Reproducibility (i.e., “inter-lab”, “inter-site”, between labs/sites)
	Lot-to-lot Reproducibility
Reagent Stability	Closed/Shelf Life

Definitions

- **Analytic validity (safety)**:
  - accuracy with which a particular genetic characteristic, such as a DNA sequence variant, chromosomal deletion, or biochemical indicator, is identified in a given laboratory test
- **Clinical validity (effectiveness)**:
  - the accuracy with which a test identifies a patient's clinical status
  - Described in terms of clinical sensitivity, specificity, positive predictive value, and negative predictive value
- **Clinical utility**:
  - the risks and benefits resulting from the use of the test

Clinical Validity - Example

- Multiple endocrine neoplasia type 2 (MEN2)
  - Autosomal dominant and confers high risk of medullary thyroid carcinoma and associated endocrine issues
  - Caused by mutations in *RET*
- 95-98% of disease causing *RET* mutations can be detected using either targeted mutation analysis or sequence analysis of select exons – **clinical sensitivity**
- **Specificity** is assumed to approach 100%, based on the high penetrance observed in MEN2 families

Moline and Eng, 2013

FDA's LDT Example

- A laboratory uses peer reviewed articles to guide development of a new diagnostic device.
- The laboratory uses general purpose reagents and analyte specific reagents combined with general laboratory instruments and develops a testing protocol, that together constitute a test system which is then verified and validated within the laboratory.
- Once validated this device is used by the laboratory to provide clinical diagnostic results.

Framework for Oversight of Laboratory Developed Tests (LDTs), Section B.

CEBPa Listing Example

test name:	CEBPalpha mutation detection
monthly volume:	5 cases/ month
intended use:	Detection of mono- or bi-allelic substitution in the CEBPA gene
clinical use:	Diagnosis of CEBPa mutated AML and prognosis
Analyte:	DNA
disease/condition:	AML
patient population:	Adults
sample type:	Blood, bone marrow
Method:	DNA sequencing
If test is a modified FDA approved test what are the modifications	N/A

Analytical Validation

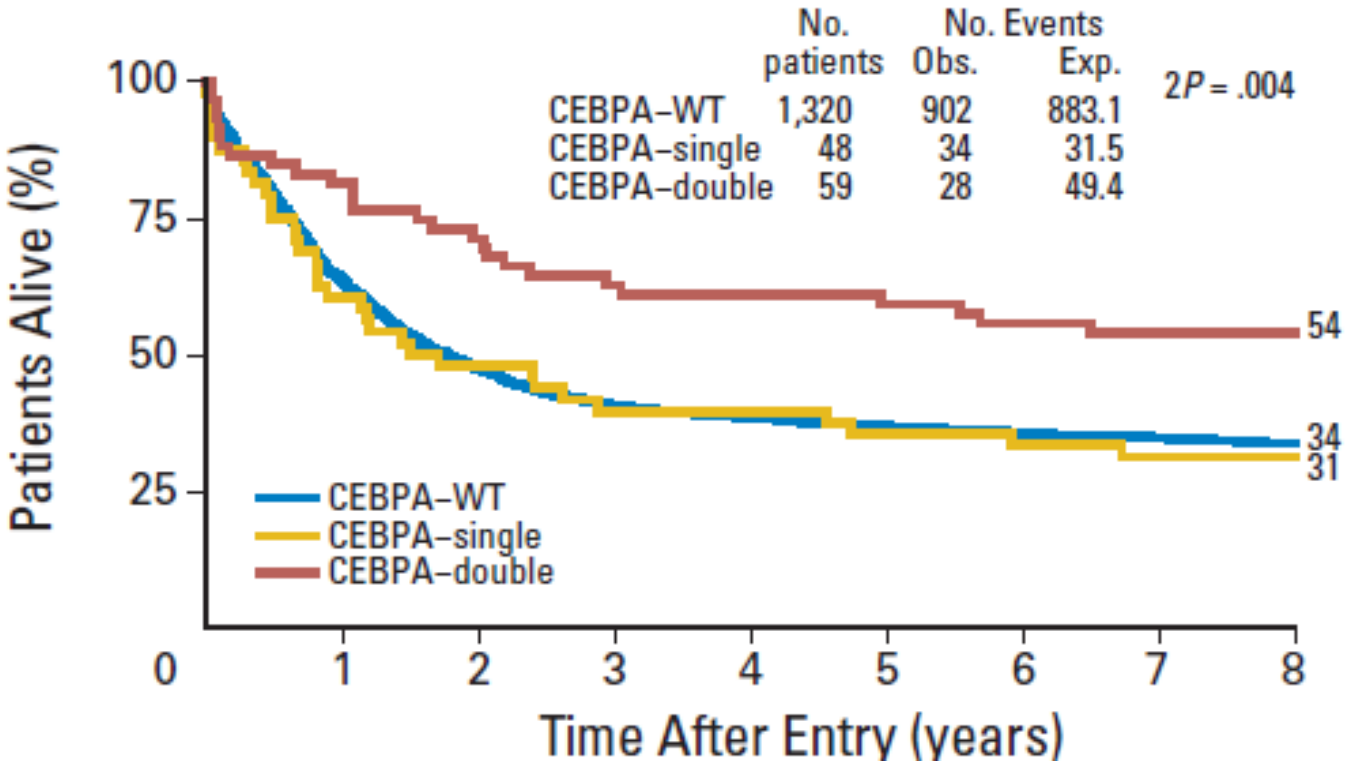
Test Performance characteristics:

Limit of Detection:	20% mutant allele frequency
Test accuracy:	100% (based upon detection of previously identified *CEBPA* mutations and SNPs)
Percent Positive Agreement:	100% (3 of 3 mutations in 2 samples)
Percent Negative Agreement:	100% (10 of 10 neg ctrl samples)
Correlation:	N/A; no method comparison undertaken
Clinical Correlation:	100% (detected both mutations in a previously tested sample from an AML patient)
Reproducibility/Precision:	Intra-assay = 100% Inter-assay = 100% Inter-technologist = 100%
Reportable ranges:	Negative/Positive (qualitative): Previously reported mutations and SNPs.

For novel variants, in silico algorithms are applied to predict the likelihood of functional impairment of the CEBPA protein ('damaging' or 'pathologic') per routine (e.g., similar to those VUS identified in muscular dystrophy gene sequencing).

Method:	Sanger Cycle sequencing, ABI 3130

Clinical Validity



- 7-15% of AMLs have CEBPA mutations (most are single mutations)
- Double mutant/biallelic cases predict a **favorable** prognosis
  - Low frequency of other mutations or other cytogenetic abnormalities

J.Clin.Onc.29.2739.2010.Green

Validation Models/Guidance

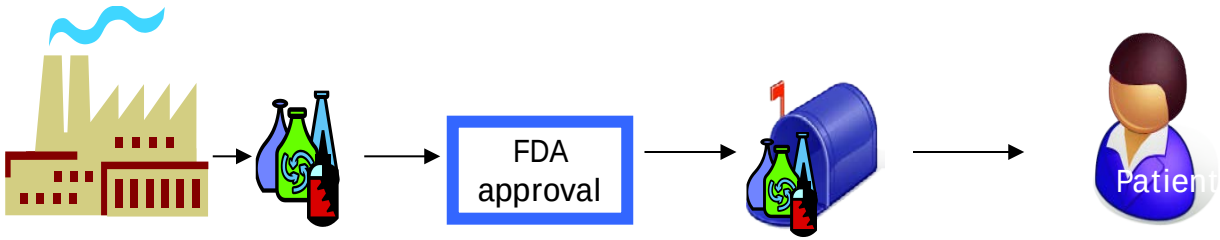
- NY State Clinical Laboratory Evaluation Program (CLEP)
  - http://www.wadsworth.org/labcert/TestApproval/forms/Submission_Guidelines_Policy.pdf
  - http://www.wadsworth.org/labcert/TestApproval/forms/Oncology_Molecular_Checklist.pdf
- Palmetto Molecular Diagnostic Services Program Clinical Test Evaluation Process (CTEP)
  - http://www.palmettogba.com/Palmetto/Moldx.Nsf/files/MolDX_Clinical_Test_Evaluation_Process_(CTEP)_M00096.pdf/$File/MolDX_Clinical_Test_Evaluation_Process_(CTEP)_M00096.pdf

Clinical Validity Documentation

- Intended use
- Indication(s) for use
- Intended use population
- Clinical Sensitivity and specificity
  - Including the positive predictive value and negative predictive value in the intended use population

Regulatory Reality

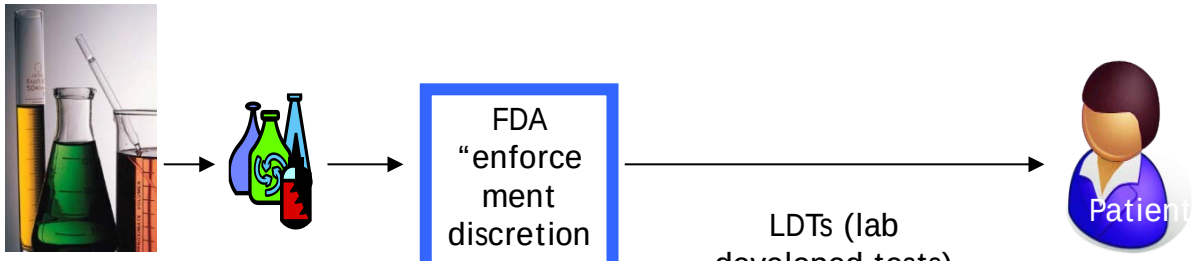
1) Commercially Distributed Test Pathway:



"test kit" manufactured for distribution to multiple labs

"Test kits" distributed to patients, hospital, or clinical lab

2) Lab Developed Test (LDT) Pathway:



Test designed, manufactured, and used in a single lab

LDTs (lab developed tests) enter the market without review

Three Pathways

1. Commercially Distributed Test Pathway

2. Lab Developed Test Pathway (Business model- single proprietary laboratories)

3. Traditional Lab Developed Test Pathway (Medical Practice – hospital laboratories)