The Squeeze on Molecular Pathology

Aaron Bossler, MD PhD

*Clinical Associate Professor, University of Iowa*
*Director, Molecular Pathology Laboratory*
*AMP Economic Affairs Committee, past-Chair*
*CAP Economic Affairs Committee, member*
*AMA Molecular Pathology Advisory Group, member*
*Pathology Coding Caucus, AMP representative*
Molecular Diagnostic Testing
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</table>
Unit of Service

One Code = One Test or Procedure = One Payment
Evolution of the Molecular and Genomic Procedure Codes

- **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

**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
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

**Payment**
- Denials due to absence of pricing
- Undervaluation
- Failure to price all codes

**Coverage**
- Local Coverage Decisions on DZ specific codes
- LCDs on entire set of codes
- MolDx Program: non-coverage due to Statutory Exclusion
- De facto National Medicare Coverage?
- Medicaid, Private Payers

*Modified from Stephen Black-Shaeffer and CAP*
### Response Comments to Draft Local Coverage Determinations

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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
## Detailed Micro-Costing Model

### DNA Extraction
- **Steps**: DNA is extracted (typically from blood or tumor)
- **Equipment**
  - Cost
  - Equipment Time (min)
  - Quantity
  - Cost per Step
  - Personnel Type
  - Hands-On Personnel Time (min)
  - Personnel Cost per Min
  - Cost per Step

### DNA Quality Control
- **Steps**: QC is done to determine the quality of each DNA sample relative to the calibrator. Adjustments may be made by dilution
- **Equipment**
  - Cost
  - Equipment Time (min)
  - Quantity
  - Cost per Step
  - Personnel Type
  - Hands-On Personnel Time (min)
  - Personnel Cost per Min
  - Cost per Step

### Library Preparation (Pre PCR)
- **Steps**: DNA targets are selected by hybridization of strand specific oligonucleotides. Here, oligonucleotide primed extension and ligation takes place. Enrichment steps may vary depending on platform. Some enrichment technologies include the Agilent SureSelect, Roche's SeqCap, RainDance Thunderstorm and Fluidigm's Access Array
- **Equipment**
  - Cost
  - Equipment Time (min)
  - Quantity
  - Cost per Step
  - Personnel Type
  - Hands-On Personnel Time (min)
  - Personnel Cost per Min
  - Cost per Step

### Library Preparation (Post PCR)
- **Steps**: Amplification by PCR adds unique barcodes to samples. Paramagnetic beads are used for cleanup prior to quantification
- **Equipment**
  - Cost
  - Equipment Time (min)
  - Quantity
  - Cost per Step
  - Personnel Type
  - Hands-On Personnel Time (min)
  - Personnel Cost per Min
  - Cost per Step

### Library Quantification & Normalization
- **Steps**: Assessment of the quality and quantity of each library prior to quantification
- **Equipment**
  - Cost
  - Equipment Time (min)
  - Quantity
  - Cost per Step
  - Personnel Type
  - Hands-On Personnel Time (min)
  - Personnel Cost per Min
  - Cost per Step

### Library Denaturing & Pooling
- **Steps**: Libraries are combined into a single pool and denatured
- **Equipment**
  - Cost
  - Equipment Time (min)
  - Quantity
  - Cost per Step
  - Personnel Type
  - Hands-On Personnel Time (min)
  - Personnel Cost per Min
  - Cost per Step

### Sequence Generation
- **Steps**: Sequencing performed on Ion Torrent, MiSeq, HiSeq, etc
- **Equipment**
  - Cost
  - Equipment Time (min)
  - Quantity
  - Cost per Step
  - Personnel Type
  - Hands-On Personnel Time (min)
  - Personnel Cost per Min
  - Cost per Step

### Documentation
- **Steps**: Recording run metrics
- **Equipment**
  - Cost
  - Equipment Time (min)
  - Quantity
  - Cost per Step
  - Personnel Type
  - Hands-On Personnel Time (min)
  - Personnel Cost per Min
  - Cost per Step

### Initial Data Review/Quality Assessment
- **Steps**: Review of FASTQ or BAM file data to ensure correct reads have been made and it is ready for further analysis using pipeline software
- **Equipment**
  - Cost
  - Equipment Time (min)
  - Quantity
  - Cost per Step
  - Personnel Type
  - Hands-On Personnel Time (min)
  - Personnel Cost per Min
  - Cost per Step

### Bioinformatics Pipeline Analysis
- **Steps**: Analysis of file using bioinformatics software
- **Equipment**
  - Cost
  - Equipment Time (min)
  - Quantity
  - Cost per Step
  - Personnel Type
  - Hands-On Personnel Time (min)
  - Personnel Cost per Min
  - Cost per Step

### Bioinformatics Output Initial Review
- **Steps**: Computer support for software
- **Equipment**
  - Cost
  - Equipment Time (min)
  - Quantity
  - Cost per Step
  - Personnel Type
  - Hands-On Personnel Time (min)
  - Personnel Cost per Min
  - Cost per Step

### Assay Gap-Filling Testing
- **Steps**: Sanger Sequencing
- **Equipment**
  - Cost
  - Equipment Time (min)
  - Quantity
  - Cost per Step
  - Personnel Type
  - Hands-On Personnel Time (min)
  - Personnel Cost per Min
  - Cost per Step

### Confirmatory Testing
- **Steps**: Sanger Sequencing
- **Equipment**
  - Cost
  - Equipment Time (min)
  - Quantity
  - Cost per Step
  - Personnel Type
  - Hands-On Personnel Time (min)
  - Personnel Cost per Min
  - Cost per Step

### Report Generation & Sign Out
- **Steps**: Comparison of data to reference gene databases
  - Generation of draft report
  - Review/Sign-out of report
- **Equipment**
  - Cost
  - Equipment Time (min)
  - Quantity
  - Cost per Step
  - Personnel Type
  - Hands-On Personnel Time (min)
  - Personnel Cost per Min
  - Cost per Step

### Data Storage
- **Steps**: Long term/Short term Data Storage of data on computers, backup systems
- **Equipment**
  - Cost
  - Equipment Time (min)
  - Quantity
  - Cost per Step
  - Personnel Type
  - Hands-On Personnel Time (min)
  - Personnel Cost per Min
  - Cost per Step

### Validation
- **Steps**: Pipeline to validate the assay (new software and test data)
- **Equipment**
  - Cost
  - Equipment Time (min)
  - Quantity
  - Cost per Step
  - Personnel Type
  - Hands-On Personnel Time (min)
  - Personnel Cost per Min
  - Cost per Step

### Maintenance
- **Steps**: 5"g care of analyzer and software systems
- **Equipment**
  - Cost
  - Equipment Time (min)
  - Quantity
  - Cost per Step
  - Personnel Type
  - Hands-On Personnel Time (min)
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---

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  - Personnel Cost per Min
  - Cost per Step

---

**Overal Total**
- **Steps**: **Totals Per Section without VMO**
- **Equipment**
  - Cost
  - Equipment Time (min)
  - Quantity
  - Cost per Step
  - Personnel Type
  - Hands-On Personnel Time (min)
  - Personnel Cost per Min
  - Cost per Step

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  - Personnel Cost per Min
  - Cost per Step

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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 (e.g., 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**
Model Framework: NSCLC

Current Care:
- EGFR and ALK Mutational Analysis

Targeted Treatment Options:
- Targeted
- Clinical Trial (Targeted)
- Non-Targeted
- Hospice

GSP Care: Genomic Sequencing Procedure (81445)

GSP Anticipated Result:
- Targeted therapy selection
- Clinical trial selection
- Non-Targeted selection
- Hospice care

Six Months
GSP Care: Additive Driver Genes to EGFR and ALK

- Neratinib
- Tivantinib
- Vandetanib
- Cabozantinib
- Crizotinib
- LDK378
- Neratinib
- Neratinib
- Tivantinib
- Vemurafenib
- Erlotinib
- Afatinib
- Gefitinib

Mutations in NSCLC
- None: 24.4%
- KRAS: 32.2%
- V600: 11.3%
- EGFR: 7.0%
- BRAF: 4.3%
- MET ex14: 11.3%
- MET amp: 8.3%
- ERBB2 amp: 0.9%
- RIT1: 2.2%
- ALK fusion: 1.3%
- RET fusion: 0.9%
- ROS1 fusion: 1.7%
- MAP2K1: 0.9%
- HRAS: 0.4%
- NRAS: 0.4%

TCGA: Nature 2014 514:262
Courtesy of Dr. Lou Staudt, NCI
# NSCLC Inputs and Impact of GSP

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<th>Input</th>
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<tr>
<td># of covered lives</td>
<td>1 million</td>
<td></td>
<td>Representative plan size</td>
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<tr>
<td>Lung cancer incidence</td>
<td>.07%</td>
<td></td>
<td>2014 NCI SEER data &amp; U.S. Census</td>
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<td># diagnosed with advanced or metastatic cancer</td>
<td>5,496</td>
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<td>Based on plan covered lives, lung cancer incidence rate &amp; percent diagnoses at stage IIIB/IV</td>
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<td>Non-targeted therapy</td>
<td>83%</td>
<td>20% (↓)</td>
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<td>Clinical trial</td>
<td>4%</td>
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<td># adverse events in patients receiving treatment</td>
<td>207</td>
<td>137 (↓)</td>
<td>Adverse event rates for pharmacologic treatments weighted by treatment utilization percentage</td>
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<td><strong>Total treatment cost</strong></td>
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<td>Weighted average of individual treatment decision pathways from published data and KOLs</td>
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<td><strong>Total cost of genetic testing</strong></td>
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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
## CMS 2016 Pricing Determinations

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<td>81161</td>
<td>DMD/BMD</td>
<td>$ 140.00</td>
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<td>81246</td>
<td>FLT3 TKD variants</td>
<td>$ 82.96</td>
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<tr>
<td>81287</td>
<td>MGMT</td>
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<td>MLH1 promoter methylation</td>
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<td>81313</td>
<td>PCA/KLK3</td>
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<td>81436</td>
<td>Hereditary colon cancer (dup/del)</td>
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<td>81445</td>
<td>Solid organ neoplasm (5-50 genes)</td>
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<td>81450</td>
<td>Hematolymphoid neoplasm (5-50 genes)</td>
<td>$ 647.75</td>
</tr>
</tbody>
</table>
**PAMA Legislation: HR 4302**

- **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

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
• 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
• 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
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

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
• 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
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
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
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
• 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.

## Analytical Verification and Validation

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<tr>
<th>Category</th>
<th>Description</th>
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<tr>
<td>Accuracy</td>
<td>Method Comparison(s)</td>
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<td></td>
<td>Specimen Types</td>
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<td>Limit of Detection</td>
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<td>Limits of Quantitation (Upper and Lower)</td>
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<td></td>
<td>Linearity and Reportable Range</td>
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<td>Minimum Input Quantity and Quality</td>
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<td>Minimum Tumor Content</td>
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<td>Analytical Specificity</td>
<td>Primer and Probe Specificity</td>
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<td>Interfering Substances</td>
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<td>Precision</td>
<td>Repeatability (i.e., “intra-run”, within run)</td>
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<td>Intermediate Precision (i.e., “inter-run”, between runs, “intralab”, within lab)</td>
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<td>Reproducibility (i.e., “inter-lab”, “inter-site”, between labs/sites)</td>
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<td>Lot-to-lot Reproducibility</td>
</tr>
<tr>
<td>Reagent Stability</td>
<td>Closed/Shelf Life</td>
</tr>
</tbody>
</table>
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.
<table>
<thead>
<tr>
<th>test name:</th>
<th>CEBPalpha mutation detection</th>
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<tr>
<td>monthly volume:</td>
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<td>intended use:</td>
<td>Detection of mono- or bi-allelic substitution in the CEBPA gene</td>
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<td>sample type:</td>
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<tr>
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<tr>
<td>If test is a modified FDA approved test what are the modifications:</td>
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</table>
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

Validation Models/Guidance

- NY State Clinical Laboratory Evaluation Program (CLEP)
  - [http://www.wadsworth.org/labcert/TestApproval/forms/Oncology_Molecular_Checklist.pdf](http://www.wadsworth.org/labcert/TestApproval/forms/Oncology_Molecular_Checklist.pdf)

- Palmetto Molecular Diagnostic Services Program Clinical Test Evaluation Process (CTEP)
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

FDA approval

“Test kits” distributed to patients, hospital, or clinical lab

Patient

2) Lab Developed Test (LDT) Pathway:

Test designed, manufactured, and used in a single lab

FDA “enforcement discretion”

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)