Molecular Diagnostics Regulation

Shifting from a Biomarker-Based Approach to an Algorithm-Based Approach

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Molecular Diagnostics

Definition & Aims

Definition

Use of DNA, RNA, and protein biomarkers to test for specific states of health, disease or risk

Aims

- ***Risk Assessment:*** determine individual's future risk of disease based on molecular biomarkers
- ***Screening:*** identify at risk individuals before clinical manifestation
- ***Diagnosis:*** determine existence and identity of disease condition
- ***Treatment Selection:*** select appropriate treatment based on patient's molecular profile
- ***Prognosis***: predict patient outcome based on molecular profile
- ***Monitoring***: evaluate effectiveness of treatment based on molecular changes

Traditional v. Molecular Diagnostics

Traditional diagnostics:

- Target known biology of a single analyte (e.g. glucose, cholesterol)

Molecular diagnostics:

- Subset of *In vitro* diagnostics (IVD)
- Often monitor dozens or even hundreds or thousands of analytes
- Complicated biological factors can be addressed
- Allows for precise clinical decision making, helping clinicians manage patients through continuum of care
- Driven by evolving algorithms

Evolution of Molecular Diagnostics & Personalized Medicine

- Shift in emphasis in medicine from reaction to prevention
- New tools to decode the human genome more rapidly, accurately and at lower costs
- Adoption of personalized medicine in research, clinical practice, and medical education

Examples of MDx technologies:

There are hundreds of examples of molecular diagnostics across this continuum.

	Risk Assessment	Screening	Diagnosis	Staging and Prognosis	Therapy Selection	Monitoring
Description	Diagnostic tests to complement traditional risk factors	Applied to high-risk patient to identify disease early	Use for definitive diagnosis and general cancer typing	Assess severity and/or risk of recurrence Inform adjuvent chemo decision	Used to predict efficacy or safety response to specific treatments	Recurrence monitoring Monotoring for treatment efficacy
Molecular Diagnostic Example	CF carrier testing BRCA1 testing	MRSA HPV	TB CT/NG	OncoType Dx MammaPrint	BRAF KRAS Her2	BCR-ABL HIV viral load

Next Generation Algorithm-Based MDx

- High-throughput sequencing technologies allows for analyses previously not possible
- Ability to analyze whole genomes, transcriptomes, exomes is implicating evolution of algorithm-based MDx
- MDx continuously updated to reflect real-time feedback from patients, software and new research

Examples of algorithm-based MDx's:

- HealthTell Immunosignaturing assay tests for early disease detection
- BloodCenter of Wisconsin Diagnostic Lab's algorithm tests markers associated with Myeloproliferative Neoplasms (MPNs)
- *and many more*

Example: HealthTell

The Process

Collect

The test is simple. The physician administered kit includes a small lancet which is used to prick the finger. A single drop of blood will then be placed on a sample collection card and mailed to HealthTell's laboratory in a self-addressed stamped envelope.

Measure

The measurement is accurate. Each blood drop will be analyzed for specific binding patterns on our proprietary peptide arrays. The patterns indicate, based on a trained algorithm, specific disease states.

Results

The results are actionable. Clinicians will use the results to help determine the next steps in the diagnostic and therapeutic continuum. Results will be provided within days from the initial sample collection to the physician.

from healthtell.com

Who regulates MDx?

FDA

- **Safety** and **effectiveness** of diagnostic test
- Design and manufacture quality of test
- Most genetic tests have not been subject to premarket review until recently
  - Laboratory- Developed Tests (LDTs) via FDA Safety & Innovation Act of 2012

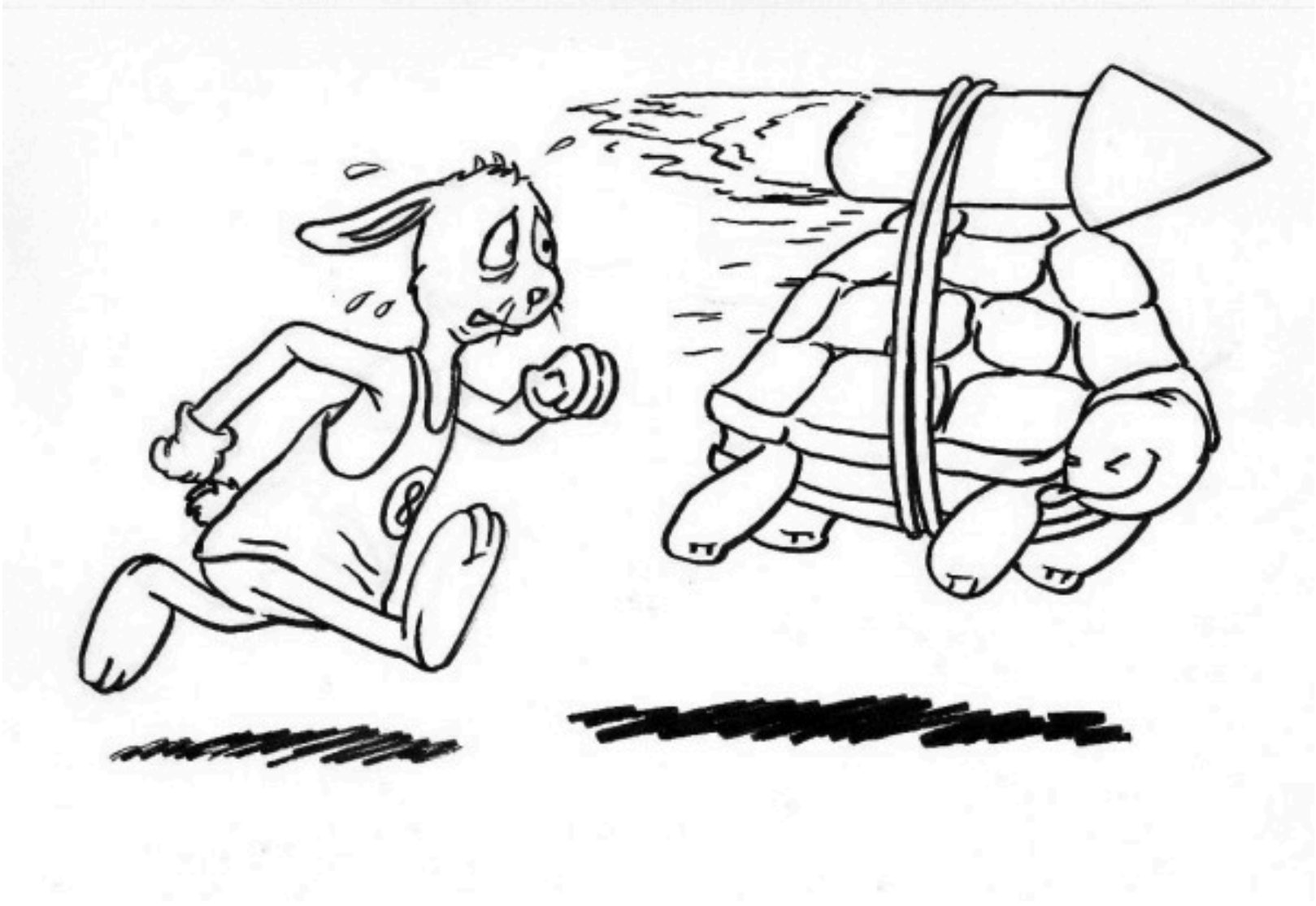
CMS (via CLIA)

- **Quality** of clinical labs and clinical testing process

Risks Assessed

- False negatives
- False positives

Challenge: MDx Technology Outpacing Regulatory Framework



Specific Challenges

- Current regulatory systems not developed to optimize regulation of MDx
  - Biomarker-based versus algorithm-based approach of FDA
- Time lag to implementation based on premarket approval and postmarket approval requirements
- Untenable for healthcare innovators
- Inhibits best patient care

Models from Other Industries

Intel's Project XL

- Project e**X**cellence & **L**eadership
- National initiative setting standard for more cost-effective public health & environmental protection
- Encourages testing of cleaner, cheaper and smarter ways to attain environmental results than under previous regulations
- Accounts for rapidly evolving algorithmic-based technology of microchips

Takeaways

- Working together with EPA to drive change
- Calling for a higher standard than previous regulations

Models from Other Industries

Autonomous Vehicles

- Rapidly evolving algorithms improving accuracy and safety of AVs
- Currently testing for driverless vehicles open only in three states: NV, FL, CA
- High efficacy (from Google's LIDAR cars):
  - 700,000 miles without an accident (compared to average U.S. driver's rate of 165,000 miles)
  - 3 recent accidents, 11 net accidents in 6 years since testing began and 1.7 million miles
- Continuous updating of LIDAR software to improve safety

Takeaways

- Similar to MDx, regulation not keeping pace with technology development
- New solutions are needed to support continued innovation & use

Federal 21st Century Cures Act: Potential Backdrop for New Regulations

- Proposed Bill from U.S. House Energy & Commerce Committee
  - Could impact every stage of innovation process and way in which FDA regulates healthcare products
  - 51-0 vote from House & Senate

- **Key Elements**
  - Re: Precision / Personalized Medicine: Calls on FDA to release information on how companies can identify subsets of a disease for purposes of advancing drug development
  - Proposes broader use of “innovative statistical methods in clinical protocols”
  - Streamlined data review

Path Forward

- Old model of one time regulatory approval of a static test no longer valid
- Need to have more dynamic system of oversight for complex molecular diagnostics based on a constantly changing algorithm
- Suggested approach:
  - Requirement for FDA notification of “significant” changes to algorithm (i.e., could affect safety or efficacy of test)
  - Notification requirement would not delay company from implementing changes
  - Some duty for ongoing after-market evaluation to ensure changes do not undermine safety/efficacy