Developing RNA-based molecular diagnostics in the post-genomic era

National Cancer Policy Forum
Policy Issues in the Development and Adoption of Molecularly Targeted Therapies for Cancer
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Introduction

• Computational biologist / translational researcher (The Cancer Genome Atlas 10,000 transcriptomes)
• Physician and clinical trialist
• Not pathologist
• Co-Founder of diagnostics company (GeneCentric)
Diagnostic Test Adoption

• Science
  – Evidence (hypothesis generation, validation)
  – Platform (tissue and technology)
• Regulatory (federal, state, accrediting bodies)
• Payment
• Practice (adoption in clinical practice)
Evidence for RNA
Mutation Detection

- Somatic (cancer causing) alterations
- Driver versus passenger
- "Mutant expression"
Structural Alteration

Detection of Structural Alterations

- Whole genome sequencing (expensive)
- Whole exome (limited)
- In situ hybridization (clinical assay, expensive and specific, “one at a time”)
- RNA – cheap and all inclusive

Structural Alterations of CDKN2A by RNA

Integrated classification beyond mutation

DNA alterations

RNA

Immune System?

Pao, Nature Medicine 2012
Clinical Validation

• Hypotheses generated (validated) in convenience datasets

• Clinical validation needs to happen in clinical trials datasets
  – Largely absent or unavailable ($)
  – Generation of new data prohibitive ($$$)
Science

Platform
Tissue Requirements and Quality: Lots of opinions, lots of experience, few published data

• % tumor
  – min and max
• Enrichment
  – macro, micro dissection
  – other
• Total amounts
  – Amplification
• Frozen vs paraffin

• Lower amounts and % tumor are useful for finding known variants (1% tumor) and signatures
• More tumor helps find new variants and signatures
Research Frozen vs Clinical Paraffin

- Classical teaching
  - RNA degrades quickly
  - Assays on frozen tissue

- Recent experience
  - Intact 200-300 bp RNA fragments remain
  - Technologies targeting 300 bp robust
Paraffin Diagnostics

Genomic Health: Oncotype DX, breast Cancer

LabCorps: HistoPlus, lung Cancer

UNC Experience = UNCSeq: LCCC1108

- DNA and RNA assays (capture)
- 1400 patients
- 10 microns tissue (500-1000 ug)
- Variety sources
  - Biopsy (core)
  - Gross resection
- FNA (no quantification)
  - TruSite
Platforms (predicate instrument)

Issues
• Regulatory clearance for RNA? Mostly no.
• Cost
• Throughput
• Availability to small and large diagnostics labs
• Bridging of “evidence” to commercial assay

Examples
• Roche LightCycler or similar
• Roche Life Technologies sequencers
• Illumina sequencers
  – miSeq, HiSeq (multiple formats), NextSeq 500
• Nanostring (FDA)
Tests need to be compliant
Compliance is complicated and expensive
Diagnostic tests may often require private sector development
FDA regulates a test is determined by how it comes to market. A test may be marketed as a commercial test "kit," a group of reagents used in the processing of genetic samples that are packaged together and sold to multiple labs. More commonly, a test comes to market as a laboratory-developed test (LDT), where the test is developed and performed by a single laboratory, and where specimen samples are sent to that laboratory to be tested. The FDA regulates only tests sold as kits and, to date, has practiced "enforcement discretion" for LDTs.

http://www.genome.gov/10002335
Take Home: 2 strategies

• LDT
  – Potentially cheap
    • IHC
    • Foundation One, Genomic Health
  – Regulatory status is unclear

• FDA
  – 510k – <$10 million (but > any R01)
  – PMA - >$10 million
# Laboratory-developed test (LDT)

**Intended**
- Diagnostics (IVDs) manufactured. Developed, validated, and offered, within a single laboratory.
- Simple, well-understood pathology tests or
- Diagnosed rare diseases
- Used in a single institution as part of patient care
- Testing outside the institution would be prohibitive to patient care (due to timing between test need and result delivery)

**Actual**
- Delivery often is by large corporations
- Test is not simple or well understood
- Disease are common (breast cancer)
- Use in patient care not always clear
- Test is not intended for a single institution but rather reference lab strategy where entire country sends test to the lab
- Common use of an LDT in place of an FDA approved assay

**Examles**
- Genomic health
- Foundation medicine
- Labcorp (many LDT’s) including GeneCentric
Payment

1. Cost of assay
2. Investment of development for private sector partners
Intellectual Property Uncertainty

• “Mayo vs Prometheus”

• “Association for Molecular Pathology v. Myriad Genetics”

• Patent office struggling in light of these decisions, and by extension those wish to develop novel tests
Test Reimbursement

• Medicare

• State by State
• Insurer by insurer
• Self pay
Adoption in clinical practice
Impact on clinical workflow
Changing Provider Behavior

• Difficult even when evidence suggests a superior test

• Cancer - multiple physicians involved
  – Subspecialists (biopsy)
  – Surgeons (biopsy and definitive surgery)
  – Med onc
    • User of diagnostic
    • Involved after biopsy / tissue processed
Pathology Workflow

• Anatomic pathologist diagnosis of cancer have short timeline
• Special tests outside workflow
  – Send out LDT
  – Molecular tests in molecular path lab
  – Default IHC (even if test is inferior)
• Lack of coordination in information management
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Carcinoma of Unknown Primary (CUP) Personal experience

- Challenging diagnosis
- Extensive IHC evaluation
- Multiple LDT RNA assays
  - bioTheranostics, Rosetta, others
  - Send out
- Frequently desired by physicians
- Never sent voluntarily by our path department
  - Lack of knowledge about the CUP assays
  - Discussed largely in negative