Considerations for Validating Your NGS LDT

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17 October 2014

Los Gatos, CA

Please note that the opinions expressed herein are my own and do not necessarily reflect those of any organization with which I am affiliated.

Prologue

- Know thy audience
  - Regulatory: FDA, CLIA (CMS), CAP, NYDOH
  - Reimbursement: CMS, MAC, commercial payer

- Know thy platform
  - Each has different strengths and weaknesses
  - Affects applicability of certain validation elements

- Know thy application
  - Focus on NGS-based oncology panels as an example
  - Nuanced differences exist for other applications, such as noninvasive prenatal screening (NIPS) or infectious disease testing

Some terms of art

- Analytical Validity (AV): How accurately and reliably does the test measure the analyte(s) of interest?

- Clinical Validity (CV): How accurately the test measure or predict the clinical outcome(s) of interest?
  - FDA: “Accuracy with which the test identifies, measures or predicts the presence or absence of a clinical condition or predisposition in a patient.”

- Clinical Utility (CU): Does use of a test change (and improve?) patient management?
  - Decision impact: Changes in provider decision-making regarding patient management
  - Clinical impact: Improvements in healthcare outcomes
  - Economic impact: Improvements in health economic outcomes
  - Versus what? Comparative effectiveness and comparative cost effectiveness

An example is worth . . . OncoType Dx Breast

- Analytical Validity (AV): How accurately and reliably does the test measure the 21 genes of interest?

- Clinical Validity (CV): How well does the score predict the average rate of distant recurrence at 10 years? Chemotherapy benefit?

- Clinical Utility (CU)
  - Decision impact: Does use of the test to guide patient management change the number of patients undergoing chemotherapy?
  - Clinical impact: Does use of the test to guide patient management decrease how many patients experience distant recurrence, or increase how many patients benefit from adjuvant chemotherapy?
  - Economic impact: Is use of the test to guide patient management cost-effective?
  - Versus what? The standard-of-care? When? (NSABP B-14 and B-20)

Some observations

- Regulatory approval ≠ payer coverage
  - FDA vs CMS: "Safety and efficacy" vs "reasonable and necessary"
  - Example: PET scans for β amyloid
    - Multiple approvals by the FDA and EMEA
    - CMS more reticent since
      - Not clear that clinical interventions effective enough to warrant scans
      - Also unclear what the intended use population should be ("patients with cognitive impairment being evaluated for Alzheimer's disease" per the FDA)
      - Unable to quantify the gain in CV (and ultimately CU)
  - "Personalized medicine" examples: Agendia's MammaPrint, XDx's AlloMap, Pathworks' Tissue of Origin, Progensa PCA3

- Coverage by 1 MAC (e.g., PGBA/MolDx) ≠ coverage by other MACs ≠ coverage by commercial payers
  - bioTheranostics Cancer Type ID, CardioDx Corus CAD, Genomic Health OncoType Dx Colon, VeraCyte Afirma

- Evidentiary standards for regulators and payers seem to be increasing while reimbursement levels flat or decreasing
  - Impacts of the Protecting Access to Medicare Act, Affordable Care Act, and Accountable Care Organizations
  - Value versus cost versus market-based reimbursement

The Frueh/Quinn Questions

1. Who should be tested and under what circumstances?
2. What does the test tell us, that we did not know without it? (CV)
3. Can we act on the information provided by the test? (CU)
4. Does the outcome change in a way we find value in, relative to the outcome(s) obtained without the test? (CU)
5. Will we act on the information provided by the test? (CU)
6. If the test is to be employed, can we afford it?

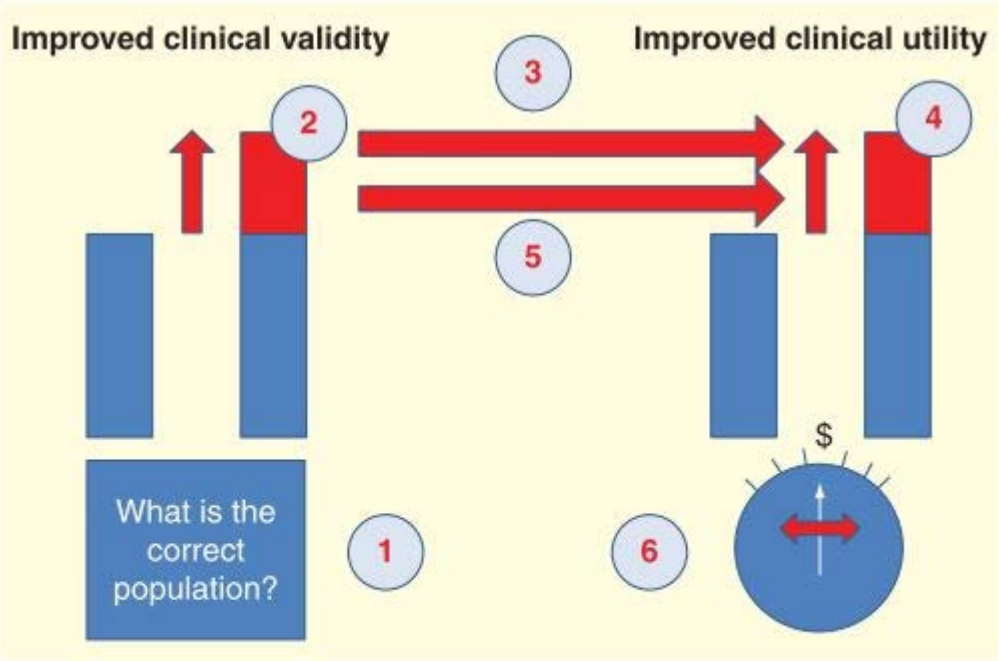

Figure 1. The gain in clinical validity directly leads, through an effect on management, to a gain in clinical utility. The incremental gain in clinical validity, like the gain in clinical utility, will be expressed against a comparator(s), in units, and with an explanation of both statistical and conceptual uncertainty.

Analytical Validity for NGS-based Oncology Panels

- Elements include:
  - Accuracy (e.g., by variant type, by tumor type, by specimen type, with representative range)
  - Analytical sensitivity (e.g., minimum input, minimum tumor content)
  - Analytical specificity (e.g., interfering substances)
  - Precision (e.g., repeatability, reproducibility, lot-to-lot)
  - Sample stability (e.g., shipping, freeze thaw)
  - Reagent stability (e.g., closed/shelf-life, open/in-use)
  - Quality control (e.g., depth of coverage, quality scores, allowable strand bias, etc)
  - Software and informatics (e.g., variant calling and clinical annotation)

- For an example, see MolDX > General > Technical Assessment (TA) Process (M00095) > NGS Validation Guidelines updated 09 Sep 2014

Clinical Validity for NGS-based Oncology Panels

- Elements include:
  - Indication(s) for use (when should test be used?)
  - Intended use population (in whom?)
  - Appropriate clinical performance metrics (e.g., clinical sensitivity and specificity, PPV and NPV in intended use population, AUROC, relative risk, odds ratio, etc.)

- Literature bridging?

- For an example, see MolDX > General > Technical Assessment (TA) Process (M00095) > NGS Validation Guidelines updated 09 Sep 2014

Clinical Utility for NGS-based Oncology Panels

- Elements include:
  - Decision impact: Does use of the test change patient management?
  - Clinical impact: Does use of the test to guide patient management improve healthcare outcomes?
    - Numerous challenging questions remain for use of NGS as a "multiplexed" or "pan" companion diagnostic (see next slide)
    - Literature bridging?
  - Economic impact: Does use of the test to guide patient management improve health economic outcomes?
    - Leverage data from drug for companion diagnostics?

Clinical Utility for NGS-based Oncology Panels

- Multiple, complex considerations can lead to analysis paralysis
  - Different uses for different alterations (e.g., predictive vs prognostic)
  - Variable “levels of evidence” for different alterations (e.g., FDA-approved, guideline recommended CoDx vs preclinical, tissue culture-based evidence of efficacy in “peer reviewed” publications)
  - The “infinite tail” of “personal” alterations
  - “Drivers” vs “passengers”
  - Inter- and intra-tumoral heterogeneity
  - “Subclinical” clones
  - Somatic vs germline alterations
  - Mutational interactions (e.g., EGFR TKIs in Kras-mutated CRC)
  - Susceptibility vs resistance mutations
  - Tissue-based vs peripheral monitoring strategies (e.g., cell-free DNA, circulating tumor cells, circulating tumor stem cells)
  - Multitude of “omes” – genome, exome, epigenome, etc

Clinical Utility for NGS-based Oncology Panels

- Is there a reasonable if imperfect path forward?
  - Ignoring (for the moment) potential implications of PAMA and FDA LDT regulation
  - Based on value vs cost or "market" (surrogate for cost?)
  - Focused on predictive (vs prognostic) alterations
  - Recognizing other potential sources of value offered by NGS
    - Better analytical performance (e.g., LOD, precision, etc) = detect primary and/or metastases sooner?
    - Lower QNS rates = more patients with results?
    - More efficient tissue usage = more patients with results, more tissue available for other/future studies?
    - Faster TAT = earlier intervention?
    - Less expensive than multi-platform (e.g., sequencing/FISH/qPCR/IHC) testing?

Clinical Utility for NGS-based Oncology Panels

- Are there FDA approved drugs targeting the gene(s) tested
  - For this patient's indication? (level 1)
  - For a different indication? (level 2 = off-label use)

- If there are no FDA approved drugs targeting the gene tested in any indication, are there clinical trials available?
  - For this patient's indication? (level 3)
  - For a different indication? (level 4)

- Other considerations
  - So what exactly is "actionable"?
  - Overlap between levels 2 and 3?
  - Restrictions on coverage and reimbursement for "investigational" or "experimental" therapies?
  - Decision impact vs clinical impact vs economic impact

Clinical Utility for NGS-based Oncology Panels

- A reality check
  - Currently, approximately 28 FDA-approved “targeted” cancer therapies (though not all specify a specific “target” under “indications and usage” in label)*
  - Against approximately 15 specific gene “targets”
  - For approximately 12 indications (per the “indications and usage” in the associated FDA label)

- But how will this scale?
  - Estimated ~950 unique clinical trials for ~460 “targeted” therapies
  - When (if?) we transition from anatomically and/or morphologically defined indications (e.g., “metastatic NSCLC”) to molecularly and/or mechanistically defined ones (e.g., “tumors with EGFR exon 19 deletions”)
    - Cautionary tale of EGFR TKIs in CRC and Kras codon 12 and 13 mutation status
    - Will the FDA drug approval process mirror such changes? Should it?

*FMI initiation report, Wedbush, 3/2014

Clinical Utility for NGS-based Oncology Panels

- So where do we “draw the line”?
  - “Social engineering” inherent in any choice
  - Can and will evolve so “perfect” need not be the enemy of “good enough”
  - There is no “right” answer, so ongoing engagement and collaboration among patients, scientists, physicians, regulators, payers, policymakers, et al will be critical.

Thank you

- Questions and comments welcome.
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