Developing Dossiers for Technical Assessment of Advanced Diagnostics

Next Generation Dx Summit 2017
Washington, D.C.

August 15, 2017
Questions Addressed

What are the standards for technical assessment of diagnostics?

Will a dossier be necessary?
What information is needed?
What standards of evidence may be applied?
What are best practices for developing dossiers?
Will a dossier be necessary?

If a dossier is needed and what it should include will depend on the overall strategy for obtaining coverage and reimbursement—one size does not fit all!

**Evidence Development**
- Clinical Studies
- Economic Models
- Supporting Evidence

**Regulatory Path**
- 510(k)
- PMA
- CE Mark
- CDx

**Coverage Determination**
- Geography (US/global)
- CMS (LCD/MolDX or NCD)
- Commercial health plans
- BCBS Evidence Street
- Hospitals/IDNs

**Reimbursement**
- Expected coding, evidence needs to support pricing & contracting
ACCE framework includes 44 questions to support evaluation of genetic tests

CMS and MolDX follow the ACCE evidence framework

| Disorder/Setting | Disease definition, epidemiology  
<table>
<thead>
<tr>
<th></th>
<th>Setting and context for diagnostic testing; clinical guidelines</th>
</tr>
</thead>
</table>
| Analytic Validity | Sensitivity, specificity, reproducibility (in the context of analysis)  
|                 | Considers pre-analytical, analytical and post-analytical stages |
| Clinical Validity | Sensitivity, specificity, reproducibility (as applied to patients & populations) |
| Clinical Utility | Natural history of the disorder  
|                 | Impact of testing on patient care  
|                 | Economic benefits of testing |
| ELSI            | Ethical, Legal, and Social Implications; including impediments, safeguards and legal issues |
AMCP Format for Formulary Submissions provides guidance for developing dossiers of tests and devices

AMCP also references ACCE, but includes additional payer considerations

<table>
<thead>
<tr>
<th></th>
<th>Product Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Product label, test characteristics</td>
</tr>
<tr>
<td></td>
<td><strong>Product comparison</strong> (alignment with primary comparators)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Disease Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Disease definition, epidemiology, pathophysiology, diagnosis, prognosis</td>
</tr>
<tr>
<td></td>
<td>Societal, humanistic and economic burden of disease</td>
</tr>
<tr>
<td></td>
<td>Treatment options</td>
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<tr>
<td></td>
<td>How the test will be used (<strong>place of the product in therapy</strong>)</td>
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</tbody>
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<table>
<thead>
<tr>
<th></th>
<th>Clinical Evidence</th>
</tr>
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<tbody>
<tr>
<td>3</td>
<td>Analytical and clinical validation studies</td>
</tr>
<tr>
<td></td>
<td>Clinical utility and health outcomes studies</td>
</tr>
<tr>
<td></td>
<td><strong>Ongoing studies</strong> and studies of investigational uses</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Economic Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>Modeling reports for <strong>budget impact</strong> and <strong>cost-effectiveness</strong> analyses</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Supporting Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>Clinical guidelines</td>
</tr>
<tr>
<td></td>
<td><strong>Compendia listings</strong> (e.g., NCCN biomarkers compendium)</td>
</tr>
<tr>
<td></td>
<td>Other <strong>health economic studies relevant to payers</strong></td>
</tr>
</tbody>
</table>

What information is necessary to include in summaries of clinical evidence in dossiers for diagnostics?

Reporting standards have been established for many study types; AMCP includes information relevant to U.S. private sector payers

<table>
<thead>
<tr>
<th>Standard</th>
<th>Information</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CONSORT</strong></td>
<td>Reporting standard designed to ensure completeness/transparency and identify potential sources of bias in randomized controlled trials</td>
</tr>
<tr>
<td><strong>STARD</strong></td>
<td>Standard for reporting diagnostic accuracy studies; 30-item checklist and flow diagram analogous to CONSORT</td>
</tr>
<tr>
<td><strong>TRIPOD</strong></td>
<td>Standard for reporting prediction models (diagnostic or prognostic); 22-item checklist and flow diagram analogous to CONSORT</td>
</tr>
<tr>
<td><strong>AMCP</strong></td>
<td>18-item checklist includes information relevant for payers, including generalizability and relevance to enrolled populations</td>
</tr>
</tbody>
</table>


TRIPOD Statement (Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis). 2015. Available at: [https://www.tripod-statement.org/](https://www.tripod-statement.org/)

What *standards of evidence* will be applied to the clinical evidence in a diagnostic dossier?

MoIDX level of evidence determination is based on study design of clinical utility studies

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
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<tbody>
<tr>
<td>3A</td>
<td>Randomized, Prospectively Controlled Trial</td>
</tr>
<tr>
<td>3B</td>
<td>Prospective-Retrospective Trial</td>
</tr>
<tr>
<td>2A</td>
<td>Prospective Observational Study</td>
</tr>
<tr>
<td>2B</td>
<td>Retrospective Data Modeling</td>
</tr>
<tr>
<td>1</td>
<td>Retrospective Observational Studies</td>
</tr>
<tr>
<td>0</td>
<td>Preclinical Studies</td>
</tr>
</tbody>
</table>

What is needed for a **budget impact model**?

Basic models consider avoided test and treatment costs, while a cost offset model may demonstrate net savings—again, one size does not fit all.

Economic Evidence

**Basic models** consider avoided test and treatment costs, while a **cost offset model** may demonstrate net savings—again, one size does not fit all. The diagram illustrates the outputs of both models.

**Outputs:**
- Net budget impact for a health plan (Total $)
- Per member, per month (PMPM)
- Per treated member, per month (PTMPM)

*Indicates the index treatment directly associated with the test result*
What is needed for a *cost-effectiveness model* (or other model types that measure benefits)?

Many options for quantifying benefits include life years or quality-adjusted life years (QALYs) gained, or natural units such as disease progression events, relapses/transmissions/hospitalizations avoided, correct diagnoses, etc.

**Cost Effectiveness**

\[
\text{Cost Effectiveness} = \sum \frac{\text{Net Costs (Test B - Test A)}}{\text{Net Benefits (Test B - Test A)}}
\]

**Estimate the costs and benefits at each of the terminal nodes in the model**

Note: Standards for conducting and reporting health economic studies are available from ISPOR and CHEERS
What **supporting evidence** may be relevant to decision makers?

Additional health economic evidence may be valuable, in particular studies that quantify economic burden and support key model inputs and assumptions.

<table>
<thead>
<tr>
<th>Supporting Evidence</th>
<th>Eligible Patient Population</th>
<th>Testing Patterns</th>
<th>Cost Studies</th>
<th>Patient-Reported Outcomes</th>
<th>Other Real-World Studies</th>
</tr>
</thead>
</table>
|                     | Epidemiology analysis or patient flow model to estimate the population to be tested | Studies reporting retrospective use of testing, association of tests with patient characteristics and subsequent treatments, etc. | Measure resource use and cost (e.g., hospitalization, treatment costs, etc.) | Assess health-related quality of life or preferences for testing/treatment | Registries (prospective observational studies)  
Chart reviews and electronic medical records  
Administrative claims  
Surveys (patient, provider, payer, etc.) |
What other evidence frameworks or formats are available?

Dossiers may be organized based on NICE single technology appraisal guidelines and EUNET HTA core model for diagnostic technologies

<table>
<thead>
<tr>
<th>Decision Problem</th>
<th>Health condition and position of the technology in the treatment pathway</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Description of technology being appraised/technical characteristics</td>
</tr>
<tr>
<td></td>
<td>Features/context for use, supplies and information required</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical Effectiveness</th>
<th>SLR to identify and select relevant studies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Summary of clinical effectiveness evidence</td>
</tr>
<tr>
<td></td>
<td>Meta-analysis; indirect and mixed treatment comparisons</td>
</tr>
<tr>
<td></td>
<td>Ongoing studies</td>
</tr>
<tr>
<td></td>
<td>Ethical/organizational/social/legal analysis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cost Effectiveness</th>
<th>SLR to identify and select cost-effectiveness studies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Economic analysis (modeling report)</td>
</tr>
<tr>
<td></td>
<td>Sensitivity and subgroup analyses</td>
</tr>
<tr>
<td></td>
<td>Documentation of clinical and economic inputs</td>
</tr>
<tr>
<td></td>
<td>Measurement and valuation of health effects (health state utilities)</td>
</tr>
</tbody>
</table>

- Note: other formats include National Association of Managed Care Physicians (NAMCP)


EUNETHTA. HTA Core Model for Diagnostic Technologies 1.0r. Available at: [http://www.eunethta.eu/outputs/hta-core-model-diagnostic-technologies-10r](http://www.eunethta.eu/outputs/hta-core-model-diagnostic-technologies-10r)

National Association of Managed Care Physicians (NAMCP) 2014. Available at: [http://www.namcp.org/journals/Medical%20Diagnostics%20Dossier.pdf](http://www.namcp.org/journals/Medical%20Diagnostics%20Dossier.pdf)
What is necessary for a compliant diagnostic dossier?

Communications between manufacturers and health care decision makers are strictly regulated

- In January 2017 the FDA issued a draft guidance for communication of health care economic information with payers that covers both drugs and devices (including dossiers)

"unbiased, factual, accurate, and non-misleading"

"based on competent and reliable scientific evidence"

"include appropriate background and contextual information"

Present "a conspicuous and prominent statement" when information is outside the approved indication

What are best practices for **business process and governance** in developing dossiers?

Best practices include a structured work plan and pre-defined accountability for dossier sections and the final submission.

**Standard Business Process for Dossiers**

1. **Planning**
   - Determine scope, logistics, responsibilities, and timeline
   - Discuss objectives, including potential positioning and key value messages

2. **Develop Content**
   - Draft disease background sections
   - Collect and summarize clinical study data
   - Develop budget impact and cost-effectiveness economic models (as appropriate)
   - Align content with objectives and key value messages

3. **Review**
   - Assemble, edit, and format dossier
   - Execute primary reviews with core team
   - Execute reviews with extended team, potentially including country affiliates

4. **Finalize**
   - Update narrative content to match final label and indication statement
   - Update models with appropriate inputs and final price
   - Conduct final reviews and disseminate

**Governance and RACI for Dossier Development**

- **1.0 Executive Summary**
  - **Project Leader**
  - **HEOR**
  - **Med Info**
  - **Clinical**
  - **Market Access**
  - **Legal**
  - **Regulatory**

- **2.0 Product/Disease Information**
  - **Raised**
  - **Acknowledge**
  - **Centralize**
  - **Centralize**
  - **Centralize**
  - **Informed**
  - **Informed**

- **3.0 Clinical Evidence**
  - **Raised**
  - **Centralize**
  - **Centralize**
  - **Centralize**
  - **Centralize**
  - **Informed**
  - **Informed**

- **4.0 Economic Value and Modeling Report**
  - **Raised**
  - **Centralize**
  - **Centralize**
  - **Centralize**
  - **Centralize**
  - **Informed**
  - **Informed**

- **5.0 Additional Supporting Evidence**
  - **Raised**
  - **Centralize**
  - **Centralize**
  - **Centralize**
  - **Centralize**
  - **Informed**
  - **Informed**

- **6.0 Dossier Appendices**
  - **Raised**
  - **Centralize**
  - **Centralize**
  - **Centralize**
  - **Centralize**
  - **Informed**
  - **Informed**

- **Final Dossier**
  - ** Raised**
  - ** Centralize**
  - ** Centralize**
  - ** Centralize**
  - ** Centralize**
  - ** Informed**
  - ** Informed**

*R=R= Responsible  A=A= Accountable  C=C= Consulted  I= Informed*
Communicating evidence to specific stakeholders may require tailoring of content

CONSIDERATIONS WHEN TAILORING DOSSIERS

How are different stakeholders impacted by costs?

For example, workflow improvements may only be experienced locally, so a cost analysis from each stakeholder highlights different components of savings.

How does each stakeholder perceive value?

Value can be expressed using many different metrics.

For example, turnaround time may be highly impactful to physicians, and ROI may be relevant for a lab director purchasing a new instrument.
A core dossier enables adaptation for multiple submissions and specific stakeholders

- Burden of disease and unmet needs articulated using consistent language and sources across multiple scientific documents
- Shared epidemiology, resource use and cost estimates for economic models
- U.S. and global submissions are tailored to specific stakeholders and aligned wherever possible with information from the core dossier
Key takeaways

The format for diagnostic dossiers may vary but the standards are generally clear:

- In the U.S., address 44 questions from ACCE and consider additional information needs of health plans outlined in the AMCP Format
- Ensure complete, transparent reporting (CONSORT, etc.)
- Ensure compliance with FDA, OIG, relevant policies

Best practices for developing a dossier includes a process and governance that adheres to these standards and meets business objectives.

Dossiers may require tailoring content, which can be facilitated by a core dossier for adaptation to U.S., global and specific stakeholders.
Contact Information

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