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Speakers

• Moderator:
  – Daryl Spinner, PhD, MBA, Managing Director, Real-World Value and Strategy, Evidera, Morrisville, NC, USA

• Panelists:
  – Brock Schroeder, PhD, Senior Director, Global Market Access Strategy and Health Economics and Outcomes Research, Illumina, San Diego, CA, USA
  – Joshua Ransom, PhD, Head of AcornAI Labs – Boston, AcornAI, a Medidata Company, Boston, MA, USA
  – Uwe Siebert, MD, MPH, MSc, ScD, Professor of Public Health, Medical Decision Making and Health Technology Assessment and Chair, Department of Public Health, University for Health Sciences, Medical Informatics, and Technology, Hall in Tirol, Austria
  – Eric Faulkner, MPH, Vice President, Precision and Transformative Medicine, Evidera, Morrisville, NC, USA
Session Agenda (1/2)

Presentations (~50-55 mins)

1. Daryl Spinner: Challenges in value demonstration and assessment of NGT to support precision medicine expansion: The need to define a path forward
2. Brock Schroeder: Addressing challenges with clinical and economic value demonstration from the NGT developer/manufacturer perspective
3. Joshua Ransom: Data challenges and opportunities to assess NGT value
4. Uwe Siebert: NGT challenges and potential approaches from the HTA perspective
5. Eric Faulkner: What health system impacts might NGT deliver? Are we ready?

Session Agenda (2/2)

Q&A Panel (~20-25 mins)

• All presenters
Housekeeping

- Thank you for holding your questions until the Q&A panel!

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Questions? Please email sigs@ispor.org.

Challenges in value demonstration and assessment of next generation testing approaches to support precision medicine expansion: The need to define a path forward

Daryl Spinner, PhD, MBA
Managing Director, Real-World Value & Strategy
Evidera | PPD

daryl.spinner@Evidera.com
+1.919.240.8408
Agenda

• What are next generation testing (NGT) approaches?

• Why is NGT different than other types of testing?

• How has NGT challenged standard value demonstration and assessment approaches?

• Where can we (ISPOR) play a role in shaping a path forward for NGT value demonstration and assessment?

What are next generation testing (NGT) approaches?

NGT approaches are thought of as tests that go beyond ‘traditional’ methods:

• Measure/ quantify multiple large molecular analytes at the same time (e.g., multiple genes, transcripts, non-self genetic material)

• Address complex questions, using ‘black box’ algorithms, and/or requiring significant expertise to interpret (e.g., etiology for a disorder w/ genetic and phenotypic heterogeneity)

• Generate lots of data (e.g., close to 1 terabyte per test run)

• More costly on a per test basis, but less costly per analyte

Examples:

• **Gene expression profiling** (e.g., 20 gene AlloMap test for heart transplant rejection)

• **Comprehensive genomic profiling** (e.g., 300+ gene FoundationOne CDx in multiple solid tumors)

• **Mendelian or whole exome or genome sequencing** (e.g., ~7,000 – 20,000 gene NGS, germline genetic diagnosis/predicting treatment response in seizure disorders, and rare diseases)

• **Multiplex infectious disease testing** (e.g., detect/ quantify multiple pathogen types in body fluids)

NGS = next generation sequencing
Why is NGT different than other types of testing?

**T**  
Targets  
Often measure multiple analytes at once, not measurable in other ways are capable of substantial multiplexing replacing multiple tests

**R**  
Results  
Driven by advanced algorithms and/or highly skilled interpretation

**I**  
Information  
Generate large amounts of data, simultaneously inform decisions around multiple diseases and/or treatment pathways approaches

**U**  
Usage  
Often leveraged for both clinical practice & research

**P**  
Platform  
Leading edge of diagnostic technology & innovation, often costlier than more traditional tests

**Versus:**  
Single or targeted/ low multiplex macromolecular analyte testing (e.g., IHC, Sanger sequencing, FISH, immunoassays, small molecule panels)

FiSH = fluorescence in situ hybridization, IHC = immunohistochemistry

Diagnostic test value is assessed by analytic, clinical and economic criteria – key questions asked by payers and assessors

<table>
<thead>
<tr>
<th>Minimum Requirements</th>
<th>Maximum Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Analytic Validity</strong></td>
<td><strong>Clinical Validity</strong></td>
</tr>
<tr>
<td>• Is the test specific, accurate, sensitive, and robust for analyte detection?</td>
<td>• Do the results correlate with the target condition in an experimental study in a representative population?</td>
</tr>
<tr>
<td>• How does its performance compare to the predecessor and/or competitors?</td>
<td>• Do the results observed early in the course of the disease correlate with a particular health outcome in an experimental study?</td>
</tr>
<tr>
<td></td>
<td>• If the test uses different methods, platforms, tissue preparation, etc than the predecessor, is that difference expected to change the patient population that is tested and/or the treatments for those patients?</td>
</tr>
<tr>
<td></td>
<td>• How many patients need to be screened to identify one patient with the disease or predisposition to the disease?</td>
</tr>
<tr>
<td></td>
<td>• What is the relative risk-benefit for conducting the test in the target population?</td>
</tr>
<tr>
<td></td>
<td>• What are the risks associated with false positive and false negative results?</td>
</tr>
<tr>
<td></td>
<td>• Does the test reduce the variability or improve prediction of healthcare utilization or costs in the target population?</td>
</tr>
<tr>
<td></td>
<td>• What is the relative cost-benefit and how does it compare to the predecessor and/or competitors?</td>
</tr>
<tr>
<td></td>
<td>• Does a reduction in false positive and false negative results reduce healthcare utilization and cost?</td>
</tr>
</tbody>
</table>

Source: Faulkner E, Spinler DS, Ransom J. Developing appropriate evidence for demonstrating the value of diagnostics: Where are we now and what is appropriate for the future state? J Managed Care Med. 2016;19:66-78.
How has NGT challenged standard value demonstration and assessment approaches?

Strain standard approaches of generating evidence & quantifying value/ impact:

• ‘Knowing’/ quality of life for patients and carers (e.g., cause of disease, reproductive planning)
• Shortened time to certainty/ complete information (e.g., upfront testing [rare pan-tumor biomarkers informing 1st-line Rx], Dx yield and circumventing Dx ‘odyssey’)
• Collecting data/ research insights and improving future patient management (e.g., reinterpretation based on updated knowledge, machine learning-based analytics)
• Routing patients to investigational therapies and trials (e.g., who receives the value?)
• Defining who is receiving and should pay for value (e.g., multiple therapies informed [developers, society])
• Incidental/ peripheral findings (e.g., non-actionable risk/ prognostic findings)
• Require longitudinality/ constructing chains of evidence across multiple datasets (e.g., in vitro lab data, epidemiological, observational, trials, claims/ health resource use)

Dx = diagnostic, Rx = therapy

Recent illustrative examples of NGT value in the literature


CGP = comprehensive genomic profiling, Dx = diagnostic, NGS = next generation sequencing, OS = overall survival, WES = whole exome sequencing
Where can we (ISPOR) play a role in shaping a path forward for NGT value demonstration and assessment?

Next step: Joint SIG effort addressing overall NGT value demonstration and assessment challenges, and an actionable path forward in a single work product

SCOPE/FOCUS: Key issues anticipated to be addressed in this work product include the following:

- How and why are NGT applications different from other diagnostic testing modalities, requiring different methods to measure and assess their value?
- What are the key novel evidentiary considerations and challenges associated with NGTs?
- What study designs and methodological solutions have been considered to address the challenges in the peer-reviewed literature and global HTAs?
- What potential gaps exist to be addressed for appropriately evaluating NGTs?
- What potential solutions may be employed, and/or further work required to fill the gaps?
- What are the implications of these findings for NGT and precision medicine stakeholders, including manufacturers, HTA bodies and payers, and for routine use by providers and patients?
- What steps and action plan would make sense to push the field forward?

Thank you for your attention!

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THANK YOU

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Clinician-reported Genetic testing Utility InDEx” (C-GUIDE) initiative on the patient-reported measure of utility is underway at the Hospital for Sick Children Research Institute and University of Toronto

Addressing challenges with clinical and economic value demonstration from the NGT developer/ manufacturer perspective

Brock Schroeder, Ph.D.
Sr Director, Market Access Strategy & HEOR
Illumina
Next Generation Sequencing Cost per Genome

Challenges with clinical and economic evidence value demonstration

- **Traditional frameworks** designed to evaluate 1 drug : 1 disease or 1 gene : 1 drug : 1 disease
- Defining and demonstrating **clinical utility** of genomic interventions—in particular across different application types (e.g., screening vs diagnostic vs predictive)
- **Intersection of clinical and research** in one test
- **Lack of standards** for assessing clinical and economic study design across different application types
- **Challenging** to perform **RCTs** for many applications
- **Balancing** standardization (e.g., IVD) with rapid progress and innovation in understanding of genomics
- **Path to clear and sustained reimbursement** is unclear
Tumor Sequencing: NGS Blurs the Boundary Between Medical Necessity and Experimental/Investigational

<table>
<thead>
<tr>
<th>Table 1 – Features of NGS conflicting with the current insurance coverage framework.</th>
</tr>
</thead>
<tbody>
<tr>
<td>NGTS feature</td>
</tr>
<tr>
<td>---------------</td>
</tr>
<tr>
<td>1. Dual utility: clinical and research</td>
</tr>
<tr>
<td>2. Informing enrollment in clinical trials</td>
</tr>
<tr>
<td>3. Comparative cost of NGTS, relative to single-gene testing</td>
</tr>
<tr>
<td>4. &quot;Sequencing pathway&quot; utility—serial use over time</td>
</tr>
<tr>
<td>5. Inherent evolutionary nature of evidence for tumor sequencing tests</td>
</tr>
<tr>
<td>6. Informing pan-cancer use of drugs</td>
</tr>
<tr>
<td>7. &quot;Many-genes-to-many-drugs&quot; utility</td>
</tr>
<tr>
<td>8. Integrative utility based on compound analysis of mutations</td>
</tr>
</tbody>
</table>

NGTS, next-generation tumor sequencing.

Moving from Challenges to Solutions

Examples of Both Innovative and Pragmatic Approaches

- Adapting clinical utility frameworks in HTA and reimbursement decision-making
- Integrating more elements of value in the evaluation of clinical utility
- Recognition of the utility and value of both clinical and research information
- Recognition of challenges & balancing progress with realities of evidence generation
- Innovative but practical contracting to drive access and RWE

Examples from 3 clinical areas

- Oncology
- Reproductive Health
- Rare and Undiagnosed Genetic Diseases
Evolving and Innovative Solutions
Adapting clinical utility frameworks

"Many genes to many drugs utility"

Genomics informing pan-cancer use of drugs

Dual Utility: clinical and research

- NCCN: “The NCCN NSCLC Guidelines Panel strongly advises broader molecular profiling with the goal of identifying rare driver mutations for which effective drugs may already be available, or to appropriately counsel patients regarding the availability of clinical trials
- Cigna rationale for change: “…facilitates assessment for appropriateness for clinical trials for some people who may not have standard evidence-based treatment options available to them”
- Economic impact of clinical trial information

Cigna (2018): "Medically necessary if medical necessity criteria are met for at least one gene on the panel"

Value in Both Clinical and Research Information
Collaboration Between a Health Plan, Oncology Practice, and Comprehensive Genomic Profiling Company from the Payer Perspective

- Early coverage of CGP in advanced cancer
- 3 year observational analysis
- Evaluated several aspects of clinical utility
- Cost diversion analysis from clinical trial enrollment
  - Savings from 6% of patients enrolling in clinical trials would have funded ~50% of the cost of CGP testing for the entire cohort
Evolving and Innovative Solutions
*Integrating more elements of value in the evaluation of clinical utility*

- Diagnostic Utility of Whole Exome / Genome Sequencing for patients with undiagnosed rare diseases

“Ending the diagnostic odyssey”

MSAC noted that the proposed main benefit of a molecular diagnosis for many patients is the cessation of further diagnostic investigations and diagnostic procedures (the ‘diagnostic odyssey’). MSAC also wanted to examine a broader assessment of the clinical utility beyond an improvement in health outcomes, to also include the “value of knowing”, reducing resources provided and time taken in the ‘diagnostic odyssey’, and the value of avoiding future children with monogenic childhood syndromes through improved family planning options.

Improvement in health outcomes included:
- Application of specific treatments as well as withholding of contraindicated treatments
- Initiation of palliative care
- Surveillance for later-onset comorbidities
- Reducing financial & psychological impact of diagnostic uncertainty

Balancing progress with the realities of evidence generation in genetic disease
*100,000 Genomes Project: Report to Parliament*

- “It has become clear that whole genomes are extraordinarily important […] we now know that, even if you want the exome, you are much better getting it from a whole genome, because it picks up inversions and quite complicated things and gives you a better-quality exome.”
- “This technology means that potentially we can diagnose any rare disease for which the genetic basis is known. That is really exciting. We have seen a huge increase in the number of patients for whom we can provide a diagnosis.”
- “Three main differences between genomic medicine and traditional healthcare that could challenge the existing contract: greater integration of, and complementarity between, healthcare and medical research; an increasing need to collect, store and share information at scale; and less certainty in how data will be used and what outcomes it will provide, due to evolving clinical practice.”
- “The 100,000 Genomes Project will not be able to provide all of the evidence required to assess the effectiveness of whole genome sequencing for all conditions.”
Evolving and Innovative Solutions
Moving past traditional frameworks

The 100,000 Genomes Project

Goal to sequence 100,000 genomes from a total of about 70,000 patients and family members, a mix of rare disease and cancer patients.

2012
100,000 Genomes project announced by UK Prime Minister David Cameron

2014
First results provided

2016
Genomics England, a company set up and owned by the UK Department of Health to run the 100,000 Genomes Project

2018
NHS commissions WGS services as a routine diagnostic test for certain rare diseases and cancers

Evolving and Innovative Solutions
Payer Partnerships to Open Access while Building Real World Evidence

Risk Sharing Contract and Real-World Clinical Utility Study with US Payer

Goal:
• Provide the type of evidence that payers and HTAs have asked for to provide coverage for NIPT in average risk pregnancies

Risk Share
• Payer opens coverage to average risk (<35y) patients
• Manufacturer will cover a portion of the downside financial risk based on agreed-upon parameters

Clinical and Economic Utility Study
• Analysis of clinical and economic outcomes from pre- to post-coverage:
  – Screening Tests
  – Invasive procedures
  – Live births
  – Fetal losses due to miscarriage
  – Fetal terminations
  – Care setting for delivery
  – Genetic counseling

Hayes
“Studies directly comparing clinical outcomes of cfDNA screening with those of routine screening strategies for low risk or general obstetric patients in a real-world setting are needed”

United Healthcare
“Prospective data is needed in which test results are acted upon clinically, showing that results lead to a change in patient management and/or outcomes. For example, data must demonstrate that physicians have sufficient confidence in both positive and negative test results to refrain from performing more invasive testing, e.g., amniocentesis, for the purpose of confirming the previously obtained test results“
Evolving and Innovative Solutions

Payer Partnerships to Open Access while Building Real World Evidence

Wednesday, 6 November
Topic: Individuals Health (PIH)
Poster #: PIH48
Location: F22

Discussion Points

Addressing challenges with clinical and economic value demonstration

- Encourage recognition of challenges with evidence development while supporting both pragmatic and innovative solutions
- Continue efforts to integrate more elements of value in the evaluation of clinical utility of novel diagnostic applications
- Establish/promote mechanisms for manufacturers and test developers to have early interaction with HTA/Payer groups → understand/discuss evidence requirements
- Identify opportunities for partnership / risk sharing
- Scaling of solutions to healthcare systems
Key Data Issues Facing Next Generation Testing

1. Volume: Data Size / Cost
2. Velocity: Complexity and Lag
3. Variability: Linkage, Aggregation, and Interoperability
4. Veracity: Availability and Reproducibility
Volume:
Genome Sequencing Costs Continue to Fall Faster than Moore’s Law – But Tech Is Not Keeping Up

Cost per Genome

Source: NHGRI

Volume & Velocity:
Genomics - The New Standard for BIG Data

### Variability:
**Data Source Variability and Interoperability**

- **Health outcomes are multifactorial**
  - Social circumstances: 15–40%
  - Environmental & physical influences: 5–20%
  - Behavior: 30–50%
  - Genetics: 20–30%
  - Medical care: 10–20%

- **Relevant data outside medical systems**
  - 60% Exogenous factors
  - 40% Endogenous factors

- **Data generated per lifetime**
  - 1,100 Terabytes
  - 6 Terabytes
  - 0.4 Terabytes

- **Genomics factors**
  - 30%
  - Per lifetime

- **Clinical factors**
  - 10%
  - Per lifetime

---

### Veracity:
**Translational & Observational Research Troubles**

#### Individual Study Bias
- Confounding
- Selection bias
- Measurement error
- Data missingness

#### Systematic Bias
- Publication bias
- P-hacking
- Data collection error
4 Evidence of Observational Research Bias


4 Systematic Comparison of Pairwise Hypertension Treatment Effects

Considerations

• Standardized Linkage between Datasets
• Semantic Interoperability
• Common Data Models
• Open Science: Prepublished, Standardized and Open Source Analysis
• Regulatory Clarity and Consistency
• Patient Consent & Privacy
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Adjunct Professor of Health Policy and Management (Harvard University)
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Acknowledgments

This work was in part supported by the ONCOTYROL Center for Personalized Cancer Medicine.

This work was supported by the COMET Center ONCOTYROL, which is funded by the Austrian Federal Ministries BMVIT/BMWFJ (via FFG) and the Tiroler Zukunftsstiftung/Standortagentur Tirol (SAT).
Overall Outline

• Challenges for Methods
  – Benefit-harm assessment
  – Cost-effectiveness assessment
  – Ethical, legal, social issues

• Challenges in Processes
  – European regulatory and HTA environment
  – Reimbursement process
  – Link from HTA to decision making

*Star Slides: for your reference

Differences to "Traditional" Diagnostics

• NGT can target diagnosis/confirmation of multiple disorders
• One disorder can have multiple targets (mutations)
• For germline mutations: potential consequences for future generations → multiple-generation time horizon
• Non-health benefits from testing (e.g., life planning)
Challenges for Benefit(-Harm) Assessment: Study Designs

• NGT
  – Can target diagnosis/confirmation of multiple disorders / mutations
  – New trial designs to address the challenges: master protocols

• Master protocols
  – New family of studies based on test-treatment combinations
  – Combine multiple sub-trials within one common protocol describing clinical, biostatistical, study management and legal aspects;
  – Parallel studies are defined by biomarker-treatment combination.
  – Common biomarker screening platform and IT infrastructure
  – Popular in oncology and hematology, of growing general interest
  – Different types: basket, umbrella, or platform trials

Master Protocols

Clinical Trials Facilitation and Coordination Group (CTFG)

Table of content
1. INTRODUCTION AND SCOPE ...................................................................................... 3
2. COMPLEX CLINICAL TRIALS - DEFINITIONS AND CONCEPTS ............................ 3
  2.1. Descriptions and concepts of complex clinical trials ............................................. 3
  2.2. Master protocols .................................................................................................. 4
  2.3. Extensive adaptive features ............................................................................... 4
  2.4. Examples of complex clinical trial designs and description of submission models .......... 4
3. POTENTIAL OPPORTUNITIES AND CHALLENGES OF COMPLEX CLINICAL TRIALS ..................................................... 6
4. KEY RECOMMENDATIONS FOR INITIATING AND CONDUCTING COMPLEX CLINICAL TRIALS ......................................................... 6
Types of Master Protocols

**Umbrella Trial**
Goal: to study *multiple targeted therapies* in the context of a *single disease*
- Biomarker-selected treatment
- Randomization or external controls
- Examples: NCI-Match Trial, BATTLE-1 Trial

**Basket Trial**
Goal: To study a *single targeted therapy* in the context of *multiple diseases/disease subtypes*
- Target-positive participants entered into trial
- Could contain multiple strata testing various biomarker-drug pairs
- Examples: B2225 Trial, BRAF V600 Trial
**Types of Master Protocols**

**Platform Trial**

Goal: To study multiple targeted therapies in the context of a single disease with "dynamic" (i.e., algorithm-based) therapies

- Perpetual manner
- Therapies allowed to enter or leave the platform
- Examples: I-SPY 2 Trial, Lung-MAP Trial

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**Examples of Master Protocols in Cancers**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Description</th>
<th>Design</th>
<th>Drug/Drugs</th>
<th>Disease and Target</th>
<th>Study Population</th>
<th>End Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCI-Match</td>
<td>Umbrella trial to determine whether treating cancers according to molecular abnormalities is effective</td>
<td>Exploratory, multicenter, noncomparative trial</td>
<td>Multiple: 30 treatments, both FDA approved and investigational, that target gene abnormalities</td>
<td>Advanced solid tumor, lymphoma, or myeloma; DNA sequencing for actionable mutations</td>
<td>35 adults planned per substudy; pediatric study to begin in 2017</td>
<td>Tumor response (primary) and progression-free survival</td>
</tr>
<tr>
<td>B225</td>
<td>Basket trial to determine cancers responsive to imatinib</td>
<td>Phase 2, multicenter, open-label, noncomparative trial</td>
<td>Single: imatinib (400 or 800 mg per day)</td>
<td>40 cancers (solid tumors and hematologic cancers) with activation of imatinib target kinases</td>
<td>186 patients ≥15 yr of age</td>
<td>Tumor response (SWOG criteria and investigator’s assessment)</td>
</tr>
</tbody>
</table>

NCI-MATCH National Cancer Institute Molecular Analysis for Therapy Choice; SWOG - Southwest Oncology Group

Woodcock, NEJM 2017
### Examples of Master Protocols in Cancers

<table>
<thead>
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</tr>
</thead>
<tbody>
<tr>
<td>I-SPY 2</td>
<td>Adaptive platform trial to identify treatment regimens for locally advanced breast cancer in the context of neoadjuvant therapy on the basis of biomarker signatures</td>
<td>Phase 2, multicenter, comparative, adaptive randomization trial</td>
<td>Multiple: standard chemotherapy and five new drugs (initially) as add-on to chemotherapy; 12 treatments tested to date, with latest (patritumab)</td>
<td>Early, high-risk breast cancer; three biomarkers (hormone-receptor status, HER2 status, and MammaPrint risk score) define eight genetic subgroups</td>
<td>1920 women (estimated) with invasive tumor ≥2.5 cm in diameter</td>
<td>Pathological complete response</td>
</tr>
<tr>
<td>Lung-MAP</td>
<td>Master protocol to evaluate biomarker-matched therapies in rare squamous-cell subsets of NSCLC</td>
<td>Phase 2–3 comparative trial</td>
<td>Multiple: four investigational drugs plus one therapy for no-match control group (initially); three investigational drugs remain</td>
<td>Squamous-cell NSCLC; multiple targets (four molecular targets initially; three remain)</td>
<td>100–170 patients planned for phase 2 (40 are now enrolled); 300–400 planned for phase 3</td>
<td>Objective response rate, progression-free survival, and overall survival</td>
</tr>
</tbody>
</table>

Lung-MAP - Lung Master Protocol; NSCLC - Non–small-cell lung cancer; HER2 - human epidermal growth factor receptor 2

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### Master Protocols

**Advantages**

- Increased genomic screening efficiency

**Challenges**

- Additional time and expertise for such complex trials

- Accelerated and streamlined clinical development timeline

- Differences in interest of (competitive) partners

- Requires collaboration of multiple industry, academic, regulatory, and community stakeholders

- Flexible objectives: explanatory and confirmatory

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Woodcock, NEJM 2017

Rentfo Ann Oncol 2017
Challenges for Cost-Effectiveness Assessment

• In principle, methods for combining diagnostic information with treatment strategies are well established
  – RCTs for "Dx-Tx packages", linked evidence, decision-analytic modeling

• NGT challenges similar to those of other diagnostic tests
  – Dealing with minor/incremental changes in Dx, matching study populations, multiple test sequence comparators, …

But ….

Challenges for Cost-Effectiveness Assessment

• Identification of multiple mutations in causative genes/incidental findings →
  Multiple different subsequent management strategies
  – This may require a different CEA approach compared to identifying a single gene at a time

• Goal of the NGT must be specific
  – If clinical practice ignores incidental finding → not included in CEA
  – If clinical practice follows-up on some/all findings → included in CEA
  – Often: multidisciplinary team meetings & collective decision on what test result should be reported

Schaafsma et al., 2009; NICE, 2011
Possible Solutions/Approaches for CEA

• Iterative (single disorder focus)
• Aggregated (multiple disorders)
• Pragmatic (a priori selection based on the expected CE impact)
• Value-of-information analysis to determine need and cost-effectiveness of further research

CEA Challenges – Specific Issues and Needs for NGT

Perspective and Outcomes
• Status Quo: Currently. healthcare perspective is dominating in NGT assessment
• Needed: Research and methods for wider array of costs and outcomes
  – E.g., NGT implications on birth decisions, insurance discrimination, privacy?

Time horizon
• Covering all downstream costs and effects for hereditary diseases
  → very long time horizon → modeling to link RCT to long-term outcomes
• Present and future trade-offs needs to be considered, discount factor?
  "Threshold time horizon"
CEA Challenges – Specific Issues and Needs for NGT

Assessment of benefits

• Difficulties in the full evaluation of the health and non-health consequences
  – Future generations implications, reproductive, lifestyle, or career decisions
• NGT for untreatable disease
  – Can still be valuable if contributes to life planning and justifying costs
  – "Plannability-adjusted life years (PALYS)"?

Assessment of harms

• Similar as for traditional diagnostic tests / screening
  – Complications/side effects of invasive follow-up and treatment → QALYs, costs
  – Overdiagnosis → usually not yet included in QALYs and costs
  – Utility and disutility for knowing disease??? Cost implications??? Who should cover?

Assessment of costs

• Status Quo: substantial variation in costs, mainly direct costs reported
• Need: Additional costs to be considered
  – Genetic counseling, subsequent treatments, clinic visits, further diagnostics
CEA Challenges – Guiding Questions

<table>
<thead>
<tr>
<th>Guiding Questions</th>
<th>Considerations</th>
</tr>
</thead>
</table>
| 1. Is the hereditary nature of the disorder known? | ➢ Defines time horizon  
➢ What if not known? Sensitivity analysis with assumed likelihoods? |
| 2. Does an effective treatment exist for the genetic disorder or associated illness? | ➢ If no treatment, health consequences are currently minimal  
➢ Sensitivity analysis to include future treatment? |
| 3. Is the individual yet to be born? | ➢ Whose health should be considered?  
➢ How to value pregnancy termination? |
| 4. Will the test identify multiple disorders and/or incidental findings? | ➢ Multiple disorders require upfront decisions of how to deal pragmatically with many management pathways |

Based on: Spackman, Genet Test Mol Bioma 2017

Challenges with Assessment of Ethical, Legal, Social and Patient Implications

• **Status Quo** on ELSI is poor
  – Only few HTA agencies (e.g., Sweden, Canada) perform ELSI assessments on regular basis  
  – But with implementation of NGT, ELSI will expand in scope and complexity
• **Whole genome sequencing (WGS) information → privacy and discrimination**
• **Patient-physician communication:** complexity increases, often not easy to explain to patients, issues with incidental findings, dis-valuing overdiagnosis
• **Equity:** unequal access, different health literacy
• **Autonomy:** right to know and right not to know, e.g., when information is relevant for relatives

Based on: Brothers, Pers Med 2015
Challenges in Processes: European Regulatory and HTA Environment

No common pathway in European regulation

- Drugs are regulated by EMA
- Companion diagnostics fall under the in-vitro diagnostic medical device regulation (IVD), which will be applied from May 2022 onward
- Notified Body must seek opinion of EMA […] on suitability of the companion diagnostics to the medicinal product
- Still, guidance for clinical evaluation in the CE-marking process of the new regulation is not yet specified.

*Challenges in Processes: HTA Environment*

- Different HTA evaluation criteria in different European countries
  - Although several countries evaluate companion diagnostics together with the drug/treatment (NICE, IQWiG), methods differ …
  - E.g. IQWiG accepts only (randomized) clinical trials with test-treatment combinations or linked evidence approaches with identical study populations for test and treatment, whereas NICE also accepts more lenient modelling approaches
  - Heterogeneity of economic evaluation across Europe: CEA, BIA, no economics
- European HTA Regulation proposal has not yet passed legislation process
  - Unclear whether evaluation of companion diagnostics included in common assessments
  - Drug evaluation would be timely after approval by EMA, but the test would be under regulation of the IVDR via a Notified Body; unclear whether a timely coordinated evaluation is possible
Challenges in Processes: Reimbursement

• Different reimbursement paths in different countries
  – often separated for hospital and outpatient settings and national and regional level
  – Reimbursement for diagnostic tests in hospital setting mostly integrated into the DRG-systems
    → procurement negotiations on regional level with hospitals, often without evidence-based decision support

• Generating evidence for NGT clinical utility is more complex, and therefore, reimbursement is uncertain

*Challenges in Processes: Reimbursement

First Recommendations:

• Robust NGT studies determining analytical & clinical validity
• System for prioritizing NGT research (quality of existing evidences)
• Engaging diverse stakeholders (HTA, larger payers) and existing evidentiary frameworks for assessing clinical utility
• Accounting for the full range of benefits (downstream effects)
Challenges in Processes: Link HTA - Decision Making

Important policy barriers (multi-stakeholder Delphi survey)

- Information proprietary and data sharing by the diagnostic companies
- Different payers have different evidentiary standards for assessing clinical utility, leading to inconsistent reimbursement policies
- Payers refuse to cover the NGT due to unclear justifications
- Lack of standardization for reporting NGT results
- Insufficient data and/or inappropriate addressing of NGT related risks (incorrect diagnosis, treatment)

Variation in coverage and reimbursement for a cohort of cancer

- # of Pts (Frequency of Reimbursement %)
  - Paid 158 Pts (26%)
  - Not Paid 446 Pts (74%)
- Non-Covered/Denied: 206 Pts (46%)
- Experimental/Investigational: 119 Pts (27%)
- Other: 66 Pts (15%)
- Unknown/NA: 39 Pts (9%)
- Medical Necessity: 16 Pts (3%)
Summary

• Challenges for Methods
  – Benefit-harm assessment
  – Cost-effectiveness assessment
  – Ethical, legal, social issues

• Challenges in Processes
  – European regulatory & HTA environment
  – Reimbursement process
  – Link from HTA to decision making

More complex, methods exists
Master protocols, overdiagnosis
Time horizon, downstream consequences, (Dis-)Utilities for knowing?
Currently poor, values for relatives
Slow and less predictable
No common EU pathway, IVD regulation
Currently uncertain, DRGs
Policy barriers, different payer standards
Eric Faulkner
Vice President, Evidera

What Health System Impacts Might Next Generation Testing Deliver?

Are We Ready?

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What kinds of health system impacts might we anticipate from the shift towards next generation testing?

1. Inform or redefine clinical pathways & improve care equity
2. Reduce or avoid the “diagnostic odyssey”
3. Bridge the continuum of care across the product lifecycle
4. Leverage broader integrated data for real time care decisions
5. Shape new clinical development models along w/RWE
6. Influence new partnership models around development and access
7. Re-channel limited hospital/health system resources
8. Redefine expectations for quality of care, efficiencies and cost flows
Are these potential health system impacts considered TODAY?

<table>
<thead>
<tr>
<th>Health System Impact</th>
<th>HTA addresses today?</th>
<th>System incentives exist today for routine consideration?</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Inform or redefine clinical pathways &amp; improve care equity</td>
<td>?</td>
<td>×</td>
</tr>
<tr>
<td>2. Reduce or avoid the “diagnostic odyssey” in complex disease scenarios</td>
<td>×</td>
<td>?</td>
</tr>
<tr>
<td>3. Dx bridge the continuum of care across the product lifecycle</td>
<td>×</td>
<td>×</td>
</tr>
<tr>
<td>4. Leverage broader data for integrated care decisions</td>
<td>×</td>
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<tr>
<td>5. Shape new clinical development models, along w/RWE</td>
<td>?</td>
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</tr>
<tr>
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<td>×</td>
<td>√</td>
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<tr>
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<td>×</td>
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</tr>
</tbody>
</table>

1. Inform clinical pathways & improve care equity

**Considered now for simpler tests**

- Sensitivity & Specificity
- Positive & Negative Predictive Value
- Patient Management
- Clinical Utility
- Prognosis or Staging Information
- ID Known Targeted Therapies

**Not generally considered by HTA**

- Value of Ruling Out (e.g., costly/targeted Tx)
- Aggregate Measures (e.g., TMB, microsatellite instability)
- ID Known Combo Tx
- ID Investigational Mono or Combo Tx

**Illustrative Questions**

1. How do we recognize the total impact potential of Next Generation Dx given the range of information?
   - For patient care?
   - For system flows?
2. When & how often to use OR mix w/simpler tests?
3. What are the safety/risks of unvalidated use? Should all information be communicated?
4. What study methods/evidence should be expected?
5. Does this broader use improve or impair equity?
Reduce or avoid the “diagnostic odyssey” in complex disease scenarios

Some patients with rare or complex diseases follow a “diagnostic odyssey” of misdiagnosis, testing, and treatment for many years. Whole genome & exome testing have been shown to reduce this experience.

Illustrative Questions

1. Should diagnostic odyssey be considered for such tests at the HTA level (where they are evaluated)?
2. If a next generation diagnostic can prevent diagnostic odyssey, what evidence base should support use?
3. Should patient- and caregiver-centric impacts be taken into account?
4. Are current “value metrics” appropriate to this scenario?

Conceptual framework showing Diagnostic Odyssey Inflection Points

Bridge the continuum of care across the product lifecycle

<table>
<thead>
<tr>
<th>Asymptomatic</th>
<th>Symptomatic</th>
<th>Disease Remission/Cure</th>
</tr>
</thead>
<tbody>
<tr>
<td>NGS circulating tumor test for routine screening of at risk patients</td>
<td>NGS for Dx &amp; oncology treatment selection</td>
<td>Simple marker or NGS monitoring</td>
</tr>
<tr>
<td>NGS for Dx &amp; oncology treatment selection</td>
<td>Antibody testing for gene modified cell therapy</td>
<td></td>
</tr>
</tbody>
</table>

- Rule out targeted Tx (e.g., EGFR, HER2, KRAS)
- Rule out IO Tx

Gene modified cell therapy indicated
4. Leverage broader integrated data for real-time care decisions (beyond our more ‘static’ approaches)

Simplified Vision for Future Dx Use

1. What does good look like?
2. Who reviews/vets for patient impact?
3. Who is responsible if something goes wrong?
4. How might this fit into cost & efficiency management approaches?

5. Shape new clinical development models, along w/RWE

Emerging New Trial Designs
- Umbrella Trial
- Basket Trial
- Adaptive Trial

Emerging New Test Approaches & Long-Acting Therapies
- NGS, Whole Genome & Exome Testing
- Cell & Gene Tx

Growing Acceptance of RWE
- Synthetic control arms
- Observational studies
- Registries
- Etc.
- US – FDA
- EU – EMA
- Canada
- China
Influence new partnership models around development and access

Illustrative HEOR Questions

1. How to we ensure that linked clinicogenomic/outcomes data are of sufficient breadth & quality?
2. What are they key health system impact questions we should consider in assessing next gen testing?
   - Which sit outside of HTA today?
   - Which may need to be included in a more comprehensive value assessment model of tomorrow?
   - What does that model look like? Who drives/is responsible?
3. What could the focus of partnerships be?
   - Genomics/outcomes linked data?
   - Clinical pathway impact & ROI analysis?
   - Measurement of broad test impacts? Quality/other dashboard? Accountable care models?

Re-channel limited hospital/health system resources

Illustrative Questions

1. What does the value of knowing and/or ruling out offer in terms of care flow decisions/efficiencies?
2. How can Dx influence decisions about when to use/not use downstream resources?
3. What implications on laboratory and staffing flows?
4. When can scarce resources be diverted?
Redefine expectations for quality of care, efficiencies and cost flows

What kinds of impacts might flow from complex diagnostics? Which of these are or should be reflected in HTA? If they are not, is there a difference evaluation & incentive structure that needs to be considered?

**Quality of Care impacts**
- Rapid & accurate diagnosis
- Rule out disease/ value of knowing
- Improve Tx selection & patient management
- Avoid ineffective or inappropriate care

**Operational efficiencies & impacts**
- Dx-influenced/driven pathways
- Improved workflow/ staff engagement
- Shift emphasis to alternative treatments/services

**Cost impacts**
- Avoid ineffective or inappropriate care
- Invest in care most likely to improve outcomes
- Avoid wastage
- Improve performance on quality & risk sharing metrics

What should we consider in bridging next generation Dx to next generation care models?

- Is our system built to measure impacts of next generation diagnostics value and risk?
- Which next generation diagnostic value drivers should we integrate into a new health value model?
- Which value drivers should/should not be considered in the province of HTA?
- For value drivers that are outside of HTA, who is responsible & what is the incentive model?
- HOW can/should ISPOR play a role here?

In the moment of crisis wise men build bridges but foolish men build dams - old Nigerian proverb
THANK YOU

• Please come to the front to leave your business card and/or use the sign-up sheet to provide your information if you are interested in joining and/or participating in our SIGs!

• Questions? Please email sigs@ispor.org.