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Improving healthcare decisions

F9: Diagnostics Evidentiary Dinosaur Evolution: Conventional Health Economics and Market Access Approaches Vs. Advanced Analytics as the New Norm?

Barcelona, Spain
Tuesday ,13 November 2018, 18:00 – 19:00, Rooms 115-116

ISPOR Special Interest Group

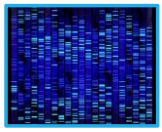
Speakers

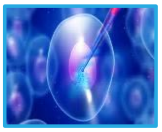
- **Eric Faulkner, MPH (moderator),** Vice President, Precision and Transformative Medicine, Evidera; Executive Director, Genomics Biotech and Emerging Technology Institute, NAMCP; Assistant Professor, Institute for Pharmacogenomics and Individualized Therapy, University of North Carolina at Chapel Hill, USA
- **Vladimir Zah, PhD, CPIAPD, BSc**, HEOR & Market Access Consultant, ISPOR Serbia, Belgrade, Serbia
- **Ken Redekop, PhD, MPH**, Associate professor, IMTA, Erasmus University, the Netherlands
- **Karsten Berndt, Dipl-Vw., MSc Epi.** HEOR+HTA & Data Science & Digitalisation Consultant; Former IVD Task Force Chair of MedTech Europe, Mannheim, Germany

Overview of the "Diagnostics Situation"

Current State

1. Rapid expansion - shift from simpler to more complex/comprehensive tests
2. Uncertainty of diagnostics evidence expectations
3. Uncertainties in biomarker validation
4. HTA agencies spending more time on Dx, but coming up a steep learning curve
5. Value-based reimbursement models do not yet apply to Dx





Future State

6. Evidence-evaluation approaches must evolve to keep pace w/broadening of test applications
7. Single-marker tests remain, but multi-marker panels & NGS proliferates as testing costs drop
8. NGS tests play a more profound role in setting treatment pathways & monitoring health state
9. AI & machine learning intersect with Dx to improve precision decision making
10. Dx may more tightly like to health system or population performance measures

Faulkner E, Poulios N, Husereau D, Zah V. Valuing precision: how will next generation diagnostics change the landscape for HEOR and patient management? International Society for Pharmacoeconomics and Outcomes Research 21th Annual International Congress, Boston, MA. May 2017.

Overview of this Forum

- (**In mere moments**) we will be **discussing several examples of molecular diagnostics ranging in complexity** – **from somewhat complex to VERY complex**
- We will be exploring and vigorously debating:
  - the extent to which our **evidence expectations & HTA approaches are aligned with these evolving test applications**
  - **OR whether we need to evolve/where or what change is required**
- We welcome you to **participate iteratively** along the way – it is more fun for us and for you!
- Also, as the moderator, I welcome you to **think of particularly difficult and vexing questions** that I can refer to our esteemed panel!

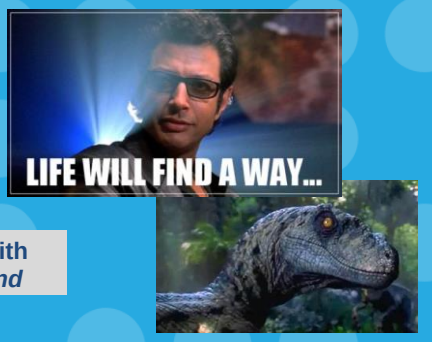


Apologies in advance for the sci-fi references you are about to endure….

SECTION

1

Complex prognostic tests…that may evolve to become predictive



Knowledge is power only if one knows what facts not to bother with
- Robert Staughton Lynd

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Prognostic testing

- **Definition:** Prognostic uses biomarkers to identify and categorize patients with different risks of disease occurrence or progression.
  - A predictive test links knowledge of biomarker status to ability to predict specific treatment outcomes
- **Common usage:** prognostic tests are commonly applied in oncology, musculoskeletal disorders and rheumatology, cardiology, neurology and obstetrics*

* Hayden JA, Cote P, Bombardier C. Evaluation of the quality of prognosis studies in systematic reviews. Ann Intern Med 2006;144:427-37

Example: Oncotype DX in Germany- Benefit assessment

- **Topic:** biomarker-based strategy to decide for or against adjuvant systemic chemotherapy vs. a biomarker-independent decision strategy or a second biomarker-based decision strategy (non-inferiority)
- **Patients:** Women with primary hormone receptor positive, HER2/new-negative breast cancer and 0 to 3 affected lymph nodes
- **Intervention:** biomarker-based strategy
- **Control:** biomarker-independent decision strategy or a second biomarker-based decision strategy
- **Outcomes:** disease-free survival

IQWiG (2018): Addendum D18-01 Version 1.1 Biomarker bei Mammakarzinom

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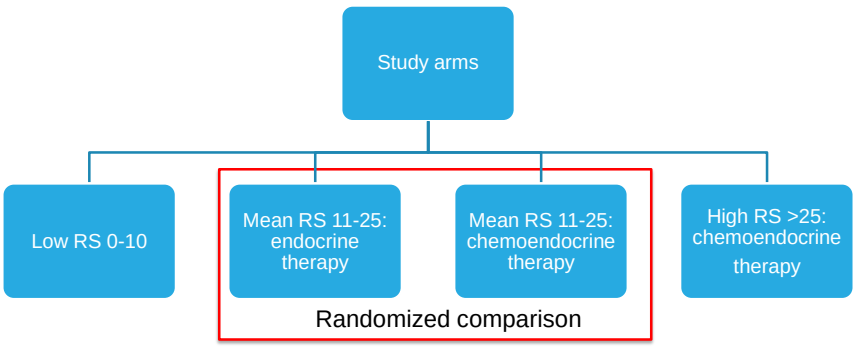
TAILORx Study: Is the endocrine therapy in patients with a mean Recurrence Score (RS) of 11 to 25 not inferior to chemoendocrine therapy for the endpoint disease-free survival.



The TAILORx study only included patients with 0 affected lymph nodes.

Adapted from: IQWiG (2018): Addendum D18-01 Version 1.1 Biomarker bei Mammakarzinom

TAILORx Study: Results for Oncotype DX

Recurrence score	Further patient characteristic	Treatment consideration
<26	older than 50 years or postmenopausal	Consider not using chemotherapy
0-10	up to 50 years or premenopausal	Consider not using chemotherapy
11-25	up to 50 years or premenopausal	Advice: use chemotherapy
>25	older than 50 years or postmenopausal	Advice: use chemotherapy

Only valid for patients with 0 affected lymph nodes.

Adapted from: IQWiG (2018): Addendum D18-01 Version 1.1 Biomarker bei Mammakarzinom

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Prognostic tests: Panel questions

- How does the system **consider a test that is prognostic for risk of disease or disease progression, but <u>may not directly</u> inform health decisions**?
  - How and to what extent is the **value of ruling out** considered?
- Can the **conventional HEOR methods sufficiently assess this technology's "value"** (including cost-effectiveness)? If not, what changes are needed?
- **Besides HEOR methods, what else needs to change** before we can assess this technology's "value"?

Prognostic tests…looking to the future of patient disease progression

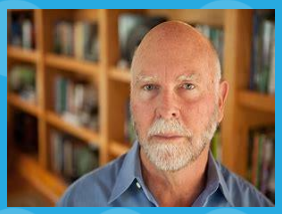
SECTION

2

Complex Next Generation Sequencing Panels

There is a long history of how DNA sequencing has improved people's lives

- J Craig Venter



Next Generation Sequencing (NGS)

- **Definition:** Term used to describe several modern sequencing technologies that enable scientists to sequence DNA and RNA at a much faster rate and more cheaply than Sanger sequencing

Driving the shift from single-marker testing to complex multi-marker testing

- **Uncertainties around expectations for validation of individual biomarkers in a test or algorithm**
- **Implications of ID'ing patient risk factors or diseases not anticipated by the test**
- **Potential for overuse, harms or ethical considerations flowing from using a precision mechanism**
- **Potential to indicate the use of more than one targeted therapy**
- **Potential to identify treatments that have not been proven in specific indication**
- **Value of the test in establishing or navigating clinical pathways**
- **Health system effects beyond standard clinical or economic metrics**

Example:

Foundation One: first FDA-approved broad companion diagnostic (CDx) that is clinically and analytically validated for solid tumors. Contains 238 cancer markers. Test is designed to provide physicians with clinically actionable information — both to consider appropriate therapies for patients and provide evidence of resistance based on the individual genomic profile of each patient's cancer. Test results include microsatellite instability (MSI) and tumor mutational burden (TMB) to help inform immunotherapy decisions

Summary: In US, Foundation One has achieved a National Coverage Policy under the Center for Medicare & Medicaid Services (CMS)

https://www.foundationmedicine.com/genomic-testing/foundation-one-cdx

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Next Generation Tests: Panel questions

- How do we **address evidence generation for tests that may cut across multiple disease areas**? What are the right study designs?
- Can the **conventional HEOR methods sufficiently assess this technology's "value"** (including cost-effectiveness)? If not, what changes are needed?
- **Besides HEOR methods, what else needs to change** before we can assess this technology's "value"?

Next generation tests make the jump to the next level…

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SECTION

3

Whole Genome Sequencing

I really think that living is going from complete certainty to complete ignorance
- Richard Dreyfuss

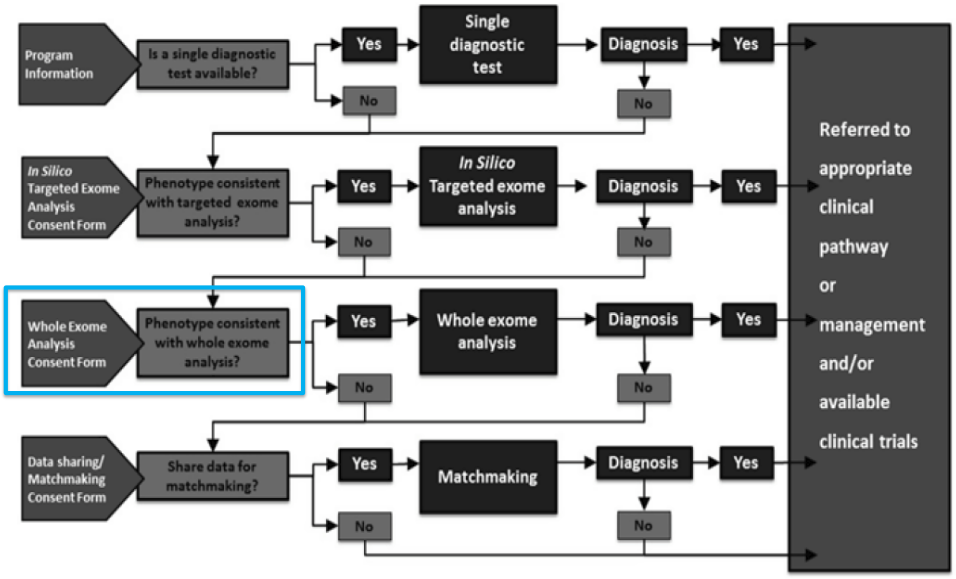
Whole Genome Sequencing: Introduction

- **Definition:** A laboratory process that is used to determine nearly all of the approximately 3 billion nucleotides of an individual's complete DNA sequence, including non-coding sequence*
- **Common usage:** WGS often utilized as an approach to rare inherited disease diagnosis, but has other applications

- **HTA of WGS diagnostic tests have challenges that set them apart from treatment HTA**
- **WGS have shared issues with other types of diagnostic tests**
- **Can advanced analytics assist with both clinical and cost-effectiveness practice?**

* National Cancer Institute - Dictionary of Genetics Terms

WGS usage example: Improved Diagnosis and Care for Rare Diseases through Implementation of Precision Public Health Framework (Australia, 2017)



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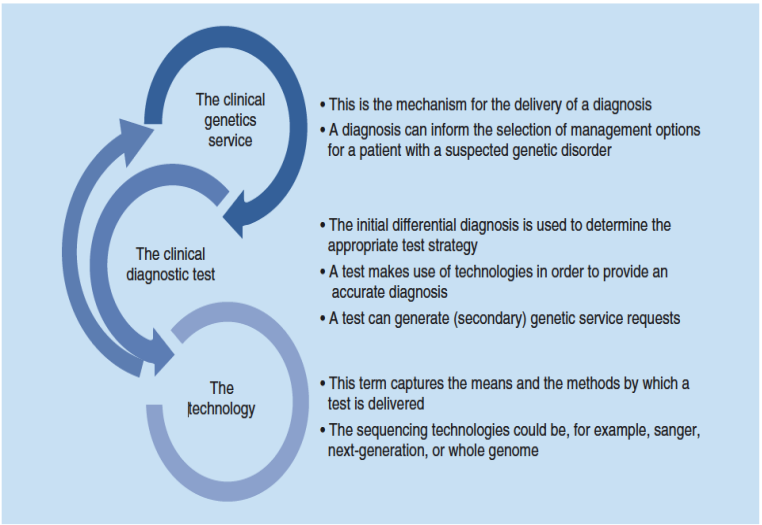
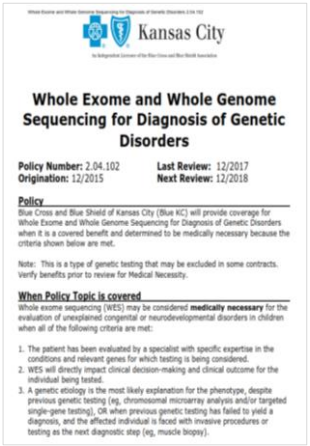
M. Posada de la Paz et al. (eds.), Rare Diseases Epidemiology: Update and Overview. Advances in Experimental Medicine and Biology 1031

WGS – link between the technology, clinical diagnostic test and service



Covered in some cases


Kansas City

Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders

Policy Number: 2.04.102 **Origination:** 12/2015 **Last Review:** 12/2017 **Next Review:** 12/2018

Policy

Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders when it is a covered benefit and determined to be medically necessary because the criteria shown below are met.

Note: This is a type of genetic testing that may be excluded in some contracts. Verify benefits prior to review for Medical Necessity.

When Policy Topic is covered

Whole exome sequencing (WES) may be considered **medically necessary** for the evaluation of unexplained congenital or neurodevelopmental disorders in children when all of the following criteria are met:

1. The patient has been evaluated by a specialist with specific expertise in the conditions and relevant genes for which testing is being considered.
2. WES will directly impact clinical decision-making and clinical outcome for the individual being tested.
3. A genetic etiology is the most likely explanation for the phenotype, despite previous genetic testing (eg, chromosomal microarray analysis and/or targeted single-gene testing), OR when previous genetic testing has failed to yield a diagnosis, and the affected individual is faced with invasive procedures or testing as the next diagnostic step (eg, muscle biopsy).

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Toward health technology assessment of whole-genome sequencing diagnostic tests: challenges and solutions. Payne K, Eden M, Davison N, https://doi.org/10.2217/pme-2016-0089

Example:

Hypothetical test for diarrhea-predominant Irritable Bowel Syndrome (IBS-D)

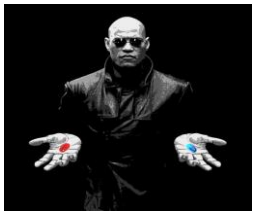
- Most trials (75% or more) show that the biomarker-based Dx approach is cost-effective above the following accuracy thresholds:
  - $100 test with 51% accuracy
  - $200 test with 57% accuracy, a $300 test with 63% accuracy
  - $400 test with 69% accuracy
  - $500 test with 76% accuracy
  - $600 test with 82% accuracy
  - $700 test with 89% accuracy
  - $800 test with 94% accuracy*

* Almario, Christopher V., Benjamin D. Noah, Alma Jusufagic, Daniel Lew, and Brennan MR Spiegel. "Cost-Effectiveness of Biomarker Tests for Irritable Bowel Syndrome With Diarrhea: A Framework for Payers." Clinical Gastroenterology and Hepatology (2018).

Whole Genome Sequencing: Panel questions

- How do we **assess the value of a technology that has the potential to predict risk across dozens of variables**, as well as **inform actionable treatment decisions under the right scenarios**?
  - How do we **address risks that we did not anticipate**?
  - How does our **definition of clinical utility shift**?
  - How often do we **deploy this technology**, including for monitoring if affordable?
- Can the **conventional HEOR methods sufficiently assess this technology's "value"** (including cost-effectiveness)? If not, what changes are needed?

Whole genome sequencing



Time to enter the Matrix…

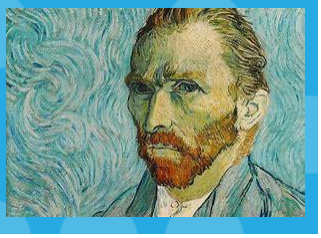
SECTION

4

Intersection of Complex Dx w/ AI & Machine Learning Decision Systems

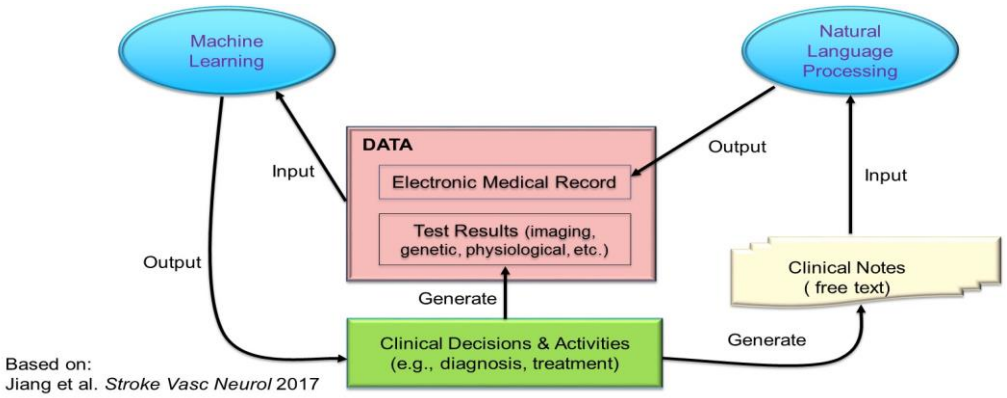
For my part, I know nothing with any certainty, but the sight of the stars makes me dream

- Vincent Van Gogh



DX + Artificial intelligence

One definition *(Merriam-Webster)*: *the capability of a machine to imitate intelligent human behavior*



Example: IBM Watson for Oncology

- Developed by IBM in partnership with the Memorial Sloan Kettering Cancer Center (MSKCC, New York, NY, USA).
- Described as a **"cognitive computing system"**
- **Provides treatment recommendations based on training from published medical literature**, publicly available treatment protocols, patient charts, test cases, and guidelines, that have been selected by **experts from MSKCC**

Ref: Gyawali, Lancet Oncol 2018

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Example: IBM Watson for Oncology

- Iterative process used to train WFO
- Cancer types include: lung, breast, cervical, ovarian, gastric, colon, rectal.
- Treatment recommendations are categorized into three groups: 'recommended treatments', treatments 'for consideration', and treatments that are 'not recommended'

- Watson for Oncology has been hailed by some for its breakthrough potential
- Others have expressed concerns about its use and validity

Ref: Somashekhar, *Ann Oncol 2018*

Dx meets AI & Machine Learning: Panel questions

- Is this **technology considered under <u>diagnostics</u>** or **<u>something else</u>**?
- Can the **conventional HEOR methods sufficiently assess this technology's "value"** (including cost-effectiveness)? If not, what changes are needed?
  - Have **evidence expectations combining diagnostic & population data been defined**?
  - How do we **validate the outputs**?
  - Does this stop at the **patient-level** or do we need to look at **system- or societal-level** impacts? Does it **change the entire HTA focus for these new applications**?
- **Besides HEOR methods, what else needs to change** before we can assess this technology's "value"?

Intersection of AI & Complex Dx:

Welcome to the Quantum Realm…

Yes, this is a picture of the tardigrade field…

SECTION

5

Conclusions and next steps for ISPOR MDD SIG

I just go where the guitar takes me…
- Angus Young

Concluding Questions

- Which **type of diagnostic** do you think will be the **next greatest challenge for global evolution of value demonstration** in the space? Why?
- If you could suggest **one improvement in global diagnostics HTA**, what would it be?

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Thank you!

Members of the Medical Device & Diagnostic Special Interest Group

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