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ISPOR MEDICAL DEVICES AND DIAGNOSTICS AND PERSONALIZED/PRECISION MEDICINE SPECIAL INTEREST GROUPS: VALUE DEMONSTRATION AND HTA OF NEXT GENERATION DIAGNOSTIC TESTING APPROACHES: CURRENT STATE AND FUTURE NEEDS FOR DRIVING PRECISION MEDICINE EXPANSION

Monday, 4 November 2019; 12:30 – 1:45 PM CET

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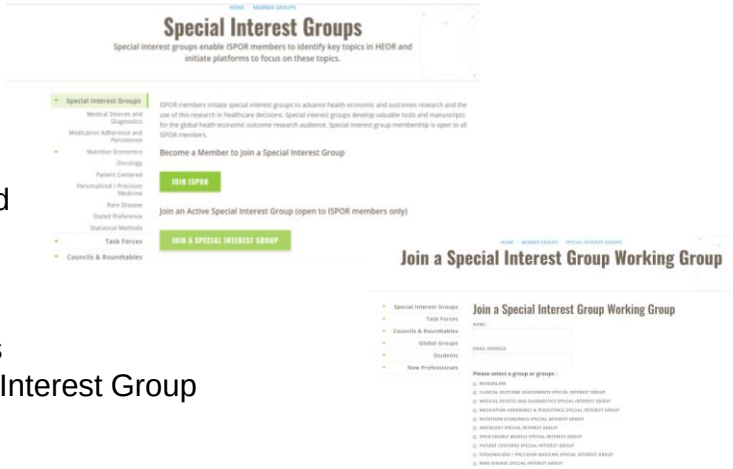

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Speakers

- **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

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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?*

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Session Agenda *(2/2)*

Q&A Panel (~20-25 mins)

- **All presenters**

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

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SECTION

1

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
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+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?

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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)*

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NGS = next generation sequencing

Why is NGT different than other types of testing?

T	R	I	U	*m*	P	*h*
Targets	**Results**	**Information**	**Usage**		**Platform**	
Often measure ***multiple analytes at once, not measurable in other ways***/ are capable of substantial multiplexing ***replacing multiple tests***	Driven by ***advanced algorithms*** and/or highly ***skilled interpretation***	Generate ***large amounts of data***, simultaneously ***inform decisions around multiple diseases and/or treatment pathways***/ approaches	Often leveraged for both ***clinical practice & research***		***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)*

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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*

Minimum Requirements → **Maximum Value**

Analytic Validity	Clinical Validity	Clinical Utility	Economic Utility
• Is the test specific, accurate, sensitive, and robust for analyte detection? • How does its performance compare to the predecessor and/or competitors?	• Do the results correlate with the target condition in an experimental study in a representative population? • Do the results observed early in the course of the disease correlate with a particular health outcome in an experimental study?	• Can the results be linked to improved health outcomes with a chain of indirect evidence? • Do test results add incremental 'nice to have' information or do they result in patient care decisions outside of standard of care?	• Can the use of the test be linked to differences in healthcare utilization or costs in the target population? • How soon after testing do those additional costs or savings accrue?
	• 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?	• In the absence of the test, how many patients remain undiagnosed or misdiagnosed? • Can the results be linked to changes in clinical management in patients with the condition?	• How are at-risk populations defined so as to limit unnecessary testing? • Does the test streamline or complicate existing treatment pathways? Does it create or reduce workstreams?
		• How many patients need to be screened to identify one patient with the disease or predisposition to the disease? • What is the relative risk-benefit for conducting the test in the target population? • What are the risks associated with false positive and false negative results?	• Does the test reduce the variability or improve prediction of healthcare utilization or costs in the target population? • What is the relative cost-benefit and how does it compare to the predecessor and/or competitors? • Does a reduction in false positive and false negative results reduce healthcare utilization and cost?

Source: Faulkner E, Spinner 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.

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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)*

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Dx = diagnostic, Rx = therapy

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Recent illustrative examples of NGT value in the literature

WES in rare disease


PLOS ONE

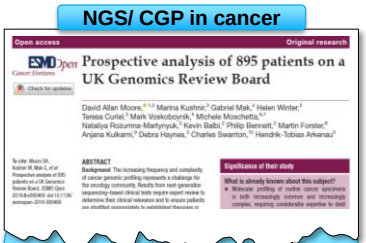
RESEARCH ARTICLE

Whole exome sequencing in neurogenetic odysseys: An effective, cost- and time-saving diagnostic approach

Time-savings w/ limited-to-no measured cost-savings *(N = 40)*

- 40% Dx yield *(16 of 40)* – no 2 w/ the same gene affected
- ~18% change in Rx *(7 of 40)*
- Avg time from symptom onset to testing = 11 yrs (3 – 42)

NGS/ CGP in cancer


Open access Original research

ESMO Open Cancer Horizons

Prospective analysis of 895 patients on a UK Genomics Review Board

David Allan Moore, Marina Kushnir, Gabriel Mak, Helen Winter, Teresa Curiel, Mark Voskoboynik, Michele Moschetta, Nataliya Rozumna-Martynyuk, Kevin Bialbi, Philip Bennett, Martin Forster, Anjana Kulkarni, Debra Haynes, Charlas Swanton, Hendrik-Tobias Arkenau

ABSTRACT

Significance of their study

What is already known about this subject?

Value of clinical trial routing

- 21% referred to specific trials *(N = 895)*
  - 7% enrolled in trials
  - 1% compassionate access

CGP in cancer


Oncotarget, 2018, Vol. 9, (No. 15), pp: 12316-12322

Research Paper

Precision oncology in advanced cancer patients improves overall survival with lower weekly healthcare costs

Derrick S. Haslem, Ingo Chakravarty, Gail Fulde, Heather Gilbert, Brian P. Tudor, Karen Lin, James M. Ford and Lincoln D. Nadauld

ABSTRACT

The impact of precision oncology on guiding treatment decisions of late-stage cancer patients was previously studied in a retrospective analysis. However, the overall

Prolonged OS associated w/ access to off-label therapy → lower weekly/ increased overall cost

- ~52 vs. 26 wks *(N = 72)*
- $2,720 vs. $3,453 wkly *(N = 44)*

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CGP = comprehensive genomic profiling, Dx = diagnostic, NGS = next generation sequencing, OS = overall survival, WES = whole exome sequencing

Sources: Cordoba et al. Whole exome sequencing in neurogenetic odysseys: An effective, cost- and time-saving diagnostic approach. PLoS One. 2018; Moore et al. Prospective analysis of 895 patients on a UK Genomics Review Board. ESMO Open. 2019; Haslem et al. Precision oncology in advanced cancer patients improves overall survival with lower weekly healthcare costs. Oncotarget. 2018.

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

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Sources: Faulkner et al. Value Health. 2012; Garfield et al. Value Health. 2016; Phillips KA. Value Health. 2018.

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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?

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Thank you for your attention!

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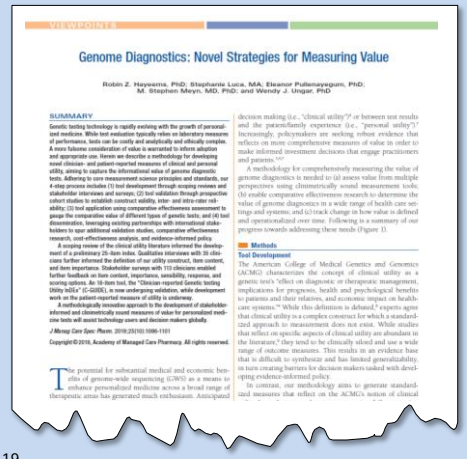
Clinician-reported Genetic testing Utility InDEx" (C-GUIDE) initiative on the patient-reported measure of utility is underway at the Hospital for Sick Children Research Institute and University of Toronto



VIEWPOINT

Genome Diagnostics: Novel Strategies for Measuring Value

Robin Z. Hayeems, PhD; Stephanie Luca, MA; Eleanor Pullenayegum, PhD; M. Stephen Meyn, MD, PhD; and Wendy J. Ungar, PhD

SUMMARY

Genetic testing technology is rapidly evolving with the growth of personalized medicine. While test evaluation typically relies on laboratory measures of performance, tests can be costly and analytically and ethically complex. A more fulsome consideration of value is warranted to inform adoption and appropriate use. Herein we describe a methodology for developing novel clinician- and patient-reported measures of clinical and personal utility, aiming to capture the informational value of genome diagnostic tests. Adhering to core measurement science principles and standards, our 4-step process includes (1) tool development through scoping reviews and stakeholder interviews and surveys, (2) tool validation through prospective cohort studies to establish construct validity, inter- and intra-rater reliability, (3) tool application using comparative-effectiveness assessment to gauge the comparative value of different types of genetic tests; and (4) tool dissemination, leveraging existing partnerships with international stakeholders to spur additional validation studies, comparative effectiveness research, cost-effectiveness analysis, and evidence-informed policy.

A scoping review of the clinical utility literature informed the development of a preliminary 25-item index. Qualitative interviews with 35 clinicians further informed the definition of our utility construct, item content, and item importance. Stakeholder surveys with 113 clinicians enabled further feedback on item content, importance, sensibility, response, and scoring options. An 18-item tool, the "Clinician-reported Genetic testing Utility indEx" (C-GUIDE), is now undergoing validation, while development work on the patient-reported measure of utility is underway.

A methodologically innovative approach to the development of stakeholder-informed and clinimetrically sound measures of value for personalized medicine tests will assist technology users and decision makers globally.

J Manag Care Spec Pharm. 2018;25(10):1098-1101

The potential for substantial medical and economic benefits of genome-wide sequencing (GWS) as a means to enhance personalized medicine across a broad range of therapeutic areas has generated much enthusiasm. Anticipated decision making (i.e., "clinical utility")[4] or between test results and the patient/family experience (i.e., "personal utility").[5] Increasingly, policymakers are seeking robust evidence that reflects on more comprehensive measures of value in order to make informed investment decisions that engage practitioners and patients.[5,6]

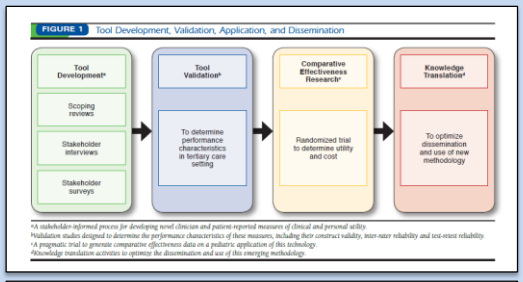
A methodology for comprehensively measuring the value of genome diagnostics is needed to (a) assess value from multiple perspectives using clinimetrically sound measurement tools; (b) enable comparative effectiveness research to determine the value of genome diagnostics in a wide range of health care settings and systems; and (c) track change in how value is defined and operationalized over time. Following is a summary of our progress towards addressing these needs (Figure 1).

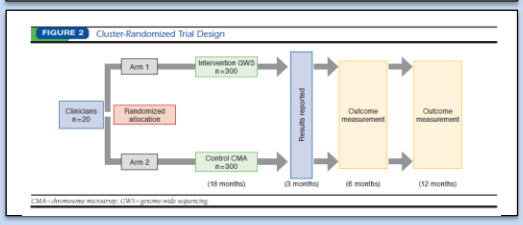
Methods

Tool Development

The American College of Medical Genetics and Genomics (ACMG) characterizes the concept of clinical utility as a genetic test's "effect on diagnostic or therapeutic management, implications for prognosis, health and psychological benefits to patients and their relatives, and economic impact on healthcare systems."[4] While this definition is debated,[6] experts agree that clinical utility is a complex construct for which a standardized approach to measurement does not exist. While studies that reflect on specific aspects of clinical utility are abundant in the literature,[7] they tend to be clinically siloed and use a wide range of outcome measures. This results in an evidence base that is difficult to synthesize and has limited generalizability, in turn creating barriers for decision makers tasked with developing evidence-informed policy.

In contrast, our methodology aims to generate standardized measures that reflect on the ACMG's notion of clinical





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Source: Hayeems et al. J Manag Care Spec Pharm. 2019.

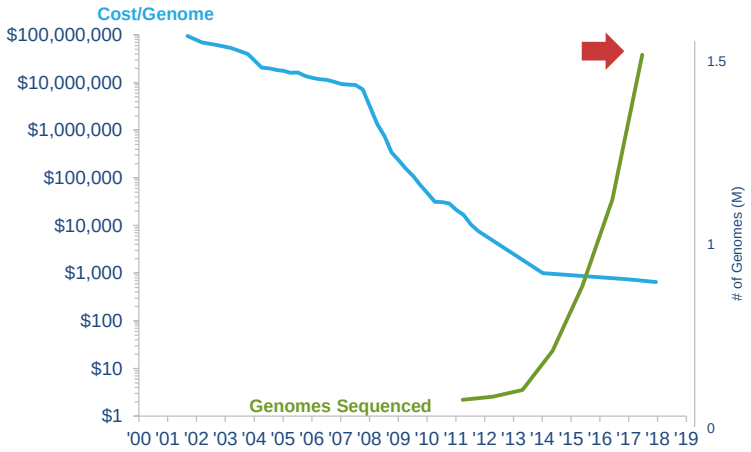
SECTION

2

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



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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

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Tumor Sequencing: NGS Blurs the Boundary Between Medical Necessity and Experimental/ Investigational

Available online at www.sciencedirect.com

ScienceDirect

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journal homepage: www.elsevier.com/locate/jval

From the Past to the Present: Insurer Coverage Frameworks for Next-Generation Tumor Sequencing

Julia R. Trosman, PhD[1,2,3,*], Christine B. Weldon, MBA[1,2,*], William J. Gradishar, MD[3], Al B. Benson III, MD[3], Massimo Cristofanilli, MD[3], Allison W. Kurian, MD, MSc[4], James M. Ford, MD[5], Alan Balch, PhD[3], John Watkins, PharmD[6], Kathryn A. Phillips[2,7]

[1]Center for Business Models in Healthcare, Glencoe, IL, USA; [2]Department of Clinical Pharmacy, UCSF Center for Translational and Policy Research on Personalized Medicine (TRANSPERS), University of California San Francisco, San Francisco, CA, USA; [3]Feinberg School of Medicine, Northwestern University, Chicago, IL, USA; [4]Stanford University School of Medicine, Stanford, CA, USA; [5]Patient Advocate Foundation, Hampton, VA, USA; [6]Premera Blue Cross, Mountlake Terrace, WA, USA; [7]Helen Diller Family Comprehensive Cancer Center, University of California San Francisco, San Francisco, CA, USA

ABSTRACT

Table 1 – Features of NGTS conflicting with the current insurance coverage framework.

NGTS feature	Conflict with the current insurance coverage framework
1. Dual utility: clinical and research	Applies to both "medically necessary" and "experimental/investigational" categories [15,16]
2. Informing enrollment in clinical trials	Clinical trial is a guideline-recommended setting for cancer treatment, and is therefore both "medically necessary" and "experimental/ investigational" [13,32]
3. Comparative cost of NGTS, relative to single-gene testing	Cost is not a formal factor of coverage framework [19,39]
4. "Sequencing pathway" utility—serial use over time	Typically focused on one technology and one point in disease trajectory [6,19]
5. Inherent evolutionary nature of evidence for tumor sequencing tests	Conflicts with the linear trajectory of evidence development and binary coverage decision [16,19]
6. Informing pan-cancer use of drugs	Conflicts with medical necessity definition for a specific indication [6,16,19,39]
7. "Many-genes-to-many-drugs" utility	Conflicts with the one-marker-one-drug evaluation of medical necessity [6,19,39]
8. Integrative utility based on compound analysis of mutations	Sequencing is considered a "bundle" of individual gene tests [15,16]

NGTS, next-generation tumor sequencing.

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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

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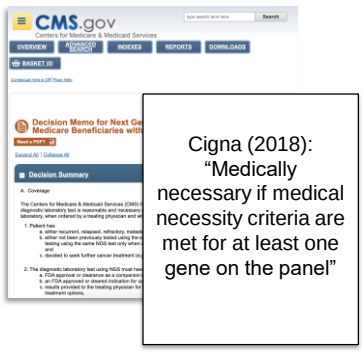
Evolving and Innovative Solutions

Adapting clinical utility frameworks

"Many genes to many drugs utility"



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

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

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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

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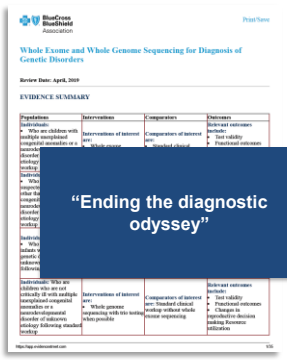
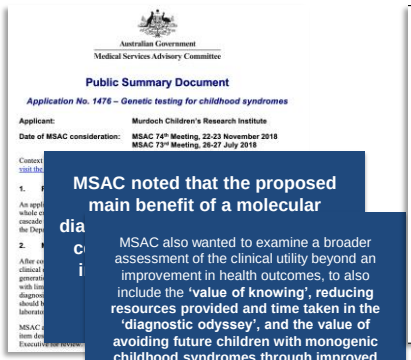
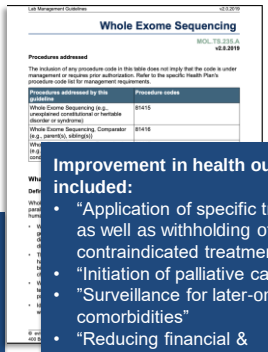
Evolving and Innovative Solutions

Integrating more elements of value in the evaluation of clinical utility

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







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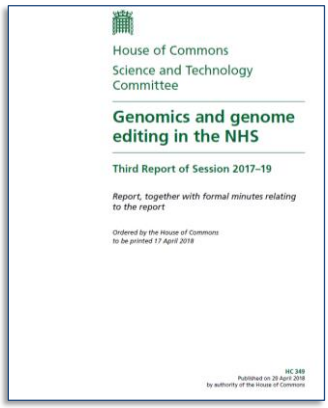
Balancing progress with the realities of evidence generation in genetic disease

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."*

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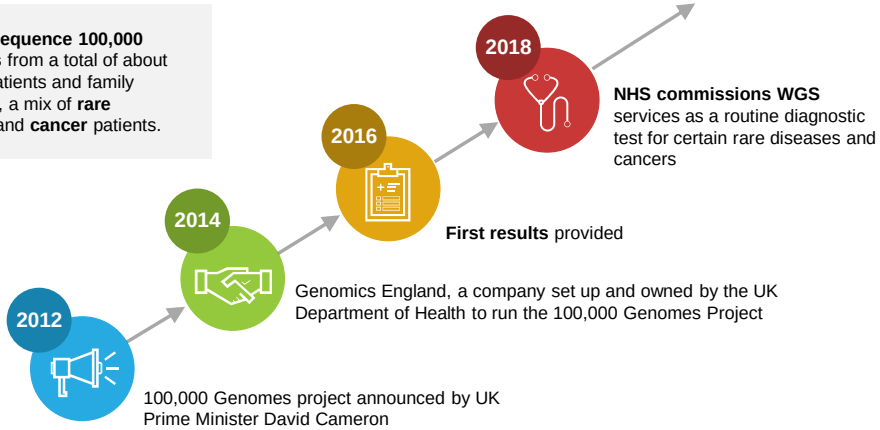
Evolving and Innovative Solutions

Moving past traditional frameworks

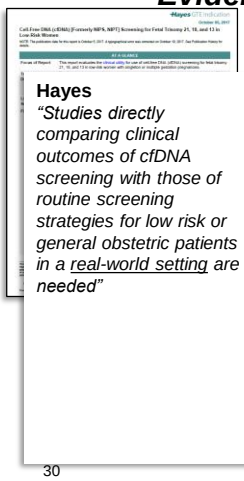
The 100,000 Genomes Project

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.



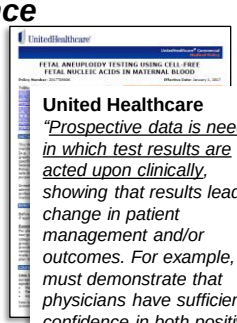
Evolving and Innovative Solutions

Payer Partnerships to Open Access while Building Real World Evidence



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"

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

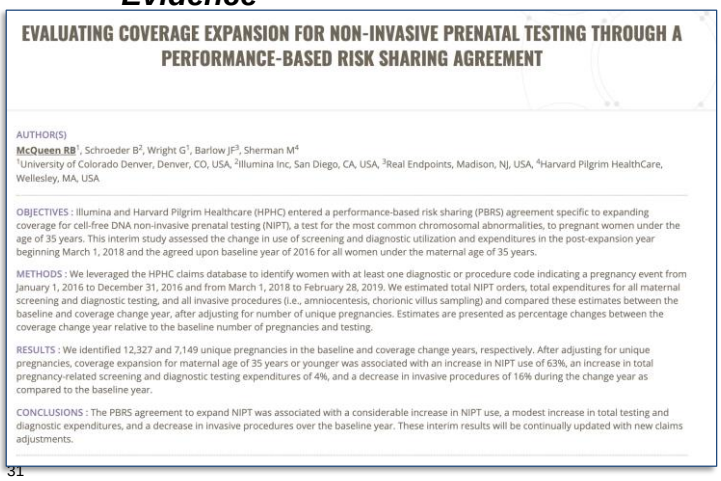
Goal:

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

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

Evolving and Innovative Solutions

Payer Partnerships to Open Access while Building Real World Evidence



EVALUATING COVERAGE EXPANSION FOR NON-INVASIVE PRENATAL TESTING THROUGH A PERFORMANCE-BASED RISK SHARING AGREEMENT

AUTHOR(S)

McQueen RB[1], Schroeder B[2], Wright G[1], Barlow JF[3], Sherman M[4]

[1]University of Colorado Denver, Denver, CO, USA, [2]Illumina Inc, San Diego, CA, USA, [3]Real Endpoints, Madison, NJ, USA, [4]Harvard Pilgrim HealthCare, Wellesley, MA, USA

OBJECTIVES : Illumina and Harvard Pilgrim Healthcare (HPHC) entered a performance-based risk sharing (PBRS) agreement specific to expanding coverage for cell-free DNA non-invasive prenatal testing (NIPT), a test for the most common chromosomal abnormalities, to pregnant women under the age of 35 years. This interim study assessed the change in use of screening and diagnostic utilization and expenditures in the post-expansion year beginning March 1, 2018 and the agreed upon baseline year of 2016 for all women under the maternal age of 35 years.

METHODS : We leveraged the HPHC claims database to identify women with at least one diagnostic or procedure code indicating a pregnancy event from January 1, 2016 to December 31, 2016 and from March 1, 2018 to February 28, 2019. We estimated total NIPT orders, total expenditures for all maternal screening and diagnostic testing, and all invasive procedures (i.e., amniocentesis, chorionic villus sampling) and compared these estimates between the baseline and coverage change year, after adjusting for number of unique pregnancies. Estimates are presented as percentage changes between the coverage change year relative to the baseline number of pregnancies and testing.

RESULTS : We identified 12,327 and 7,149 unique pregnancies in the baseline and coverage change years, respectively. After adjusting for unique pregnancies, coverage expansion for maternal age of 35 years or younger was associated with an increase in NIPT use of 63%, an increase in total pregnancy-related screening and diagnostic testing expenditures of 4%, and a decrease in invasive procedures of 16% during the change year as compared to the baseline year.

CONCLUSIONS : The PBRS agreement to expand NIPT was associated with a considerable increase in NIPT use, a modest increase in total testing and diagnostic expenditures, and a decrease in invasive procedures over the baseline year. These interim results will be continually updated with new claims adjustments.

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

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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

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SECTION

3

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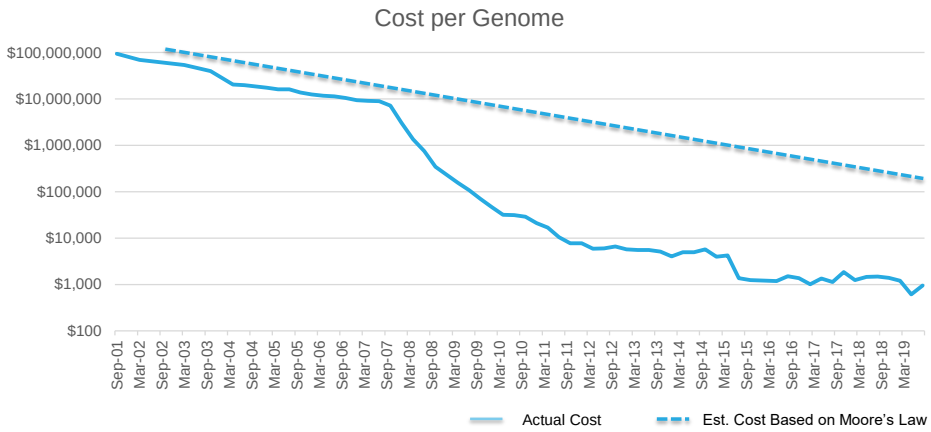
Data Challenges and Opportunities to Assess NGT Value

Joshua Ransom, PhD
Head of AcornAI Labs – Boston, AcornAI, a Medidata Company

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**

1 Volume: Genome Sequencing Costs Continue to Fall Faster than Moore's Law – But Tech Is Not Keeping Up



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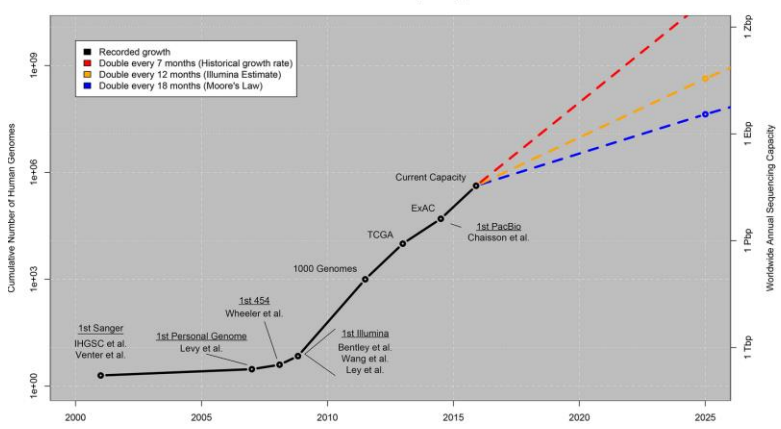
Source: NHGRI

1 2 Volume & Velocity: Genomics - The New Standard for BIG Data



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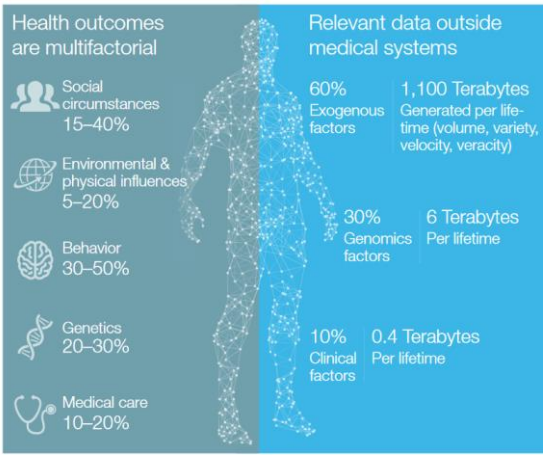
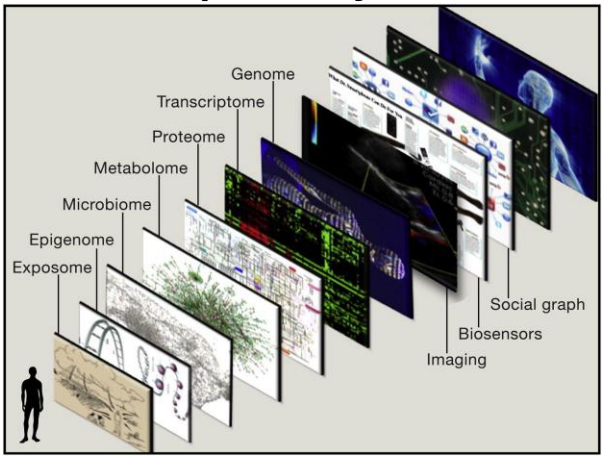
Source: Stephens ZD, et al. "Big Data: Astronomical or Genomical?" PLOS 2015

3 Variability: Data Source Variability and Interoperability





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Source: Health policy brief : "The relative contribution of multiple determinants to health outcomes," Health Affairs, August 21, 2014
Topol E. "Individualized Medicine from Prewomb to Tomb" Cell Volume 157, ISSUE 1, P241-253, March 27, 2014

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4 Veracity: Translational & Observational Research Troubles

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

Systematic Bias
- Publication bias
- P-hacking
- Data collection error

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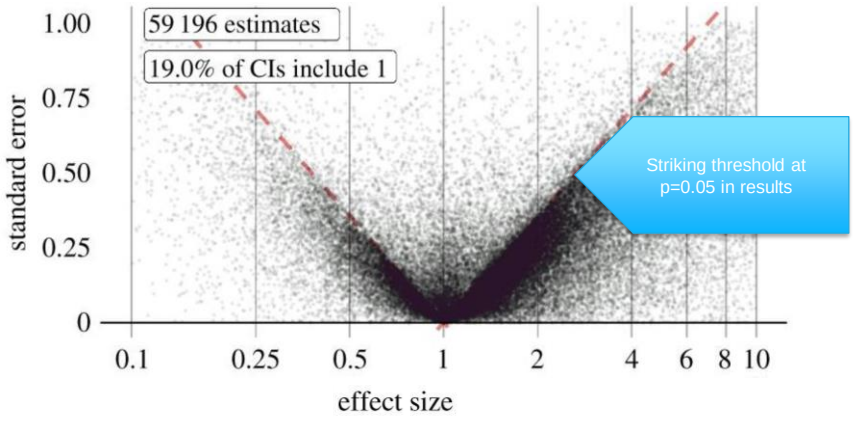
4 Evidence of Observational Research Bias



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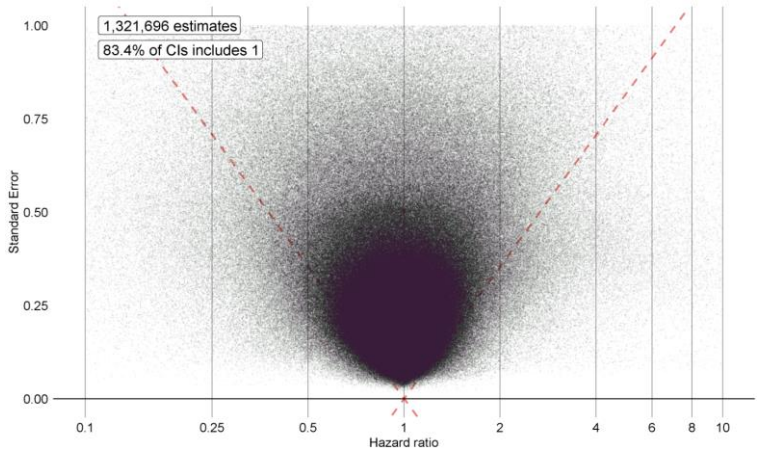
Source: Schumie MJ, et al. Phil Trans A Math Phys Eng Sci, 2018

4 Systematic Comparison of Pairwise Hypertension Treatment Effects



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Source: Schumie MJ, et al. Phil Trans A Math Phys Eng Sci, 2018

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

SECTION

4

ISPOR MEDICAL DEVICES AND DIAGNOSTICS AND PERSONALIZED/PRECISION MEDICINE SPECIAL INTEREST GROUPS: VALUE DEMONSTRATION AND HTA OF NEXT GENERATION DIAGNOSTIC TESTING APPROACHES: CURRENT STATE AND FUTURE NEEDS FOR DRIVING PRECISION MEDICINE EXPANSION.

ISPOR Europe 2019. 4 Nov. 2019, Copenhagen, Denmark

Next Generation Testing Challenges and Potential Approaches from the HTA Perspective

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Acknowledgments

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Center for Personalized Cancer Medicine

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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

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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)

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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

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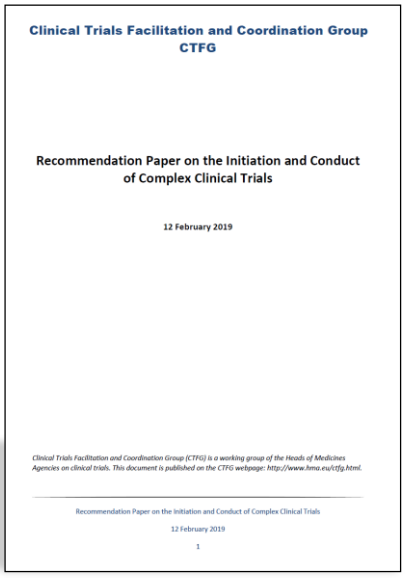
Master Protocols

Clinical Trials Facilitation and Coordination Group CTFG

Table of content


Clinical Trials Facilitation and Coordination Group
CTFG

Recommendation Paper on the Initiation and Conduct of Complex Clinical Trials

12 February 2019

Clinical Trials Facilitation and Coordination Group (CTFG) is a working group of the Heads of Medicines Agencies on clinical trials. This document is published on the CTFG webpage: http://www.hma.eu/ctfg.html.

Recommendation Paper on the Initiation and Conduct of Complex Clinical Trials
12 February 2019
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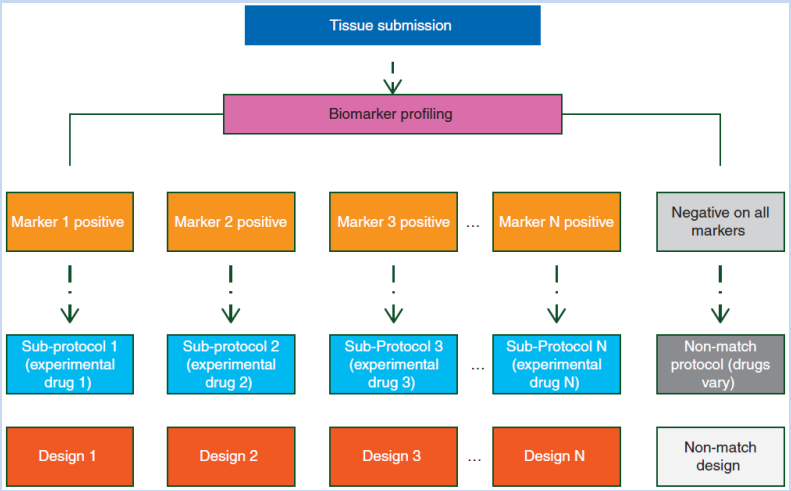
*General scheme of a Master Protocol



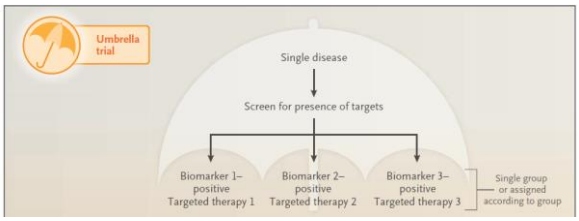
Renfro Ann Oncol 2017

Types of Master Protocols

Umbrella Trial

Goal: to study multiple targeted therapies in the context of a single disease

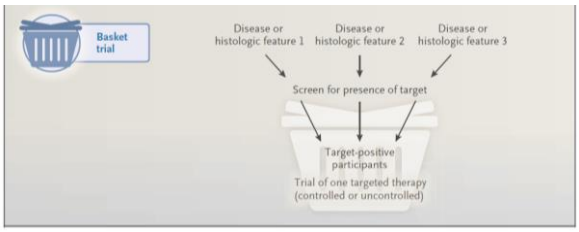
- Biomarker-selected treatment
- Randomization or external controls
- Examples: NCI-Match Trial, BATTLE-1 Trial



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



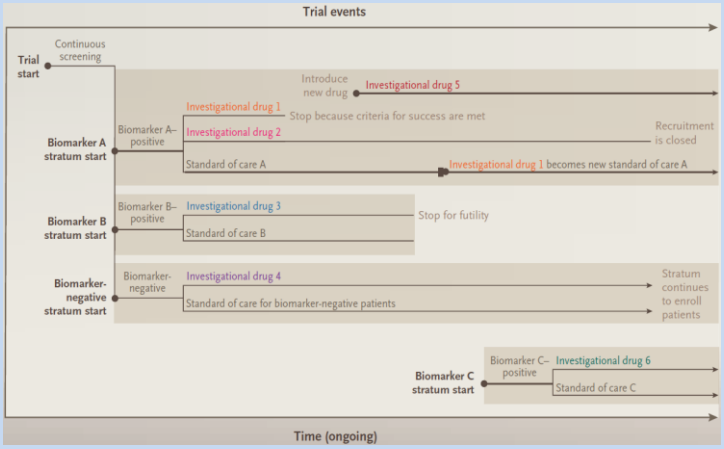
Woodcock , NEJM 2017

*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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Woodcock , NEJM 2017

*Examples of Master Protocols in Cancers

Trial	Description	Design	Drug/Drugs	Disease and Target	Study Population	End Points
NCI-Match	Umbrella trial to determine whether treating cancers according to molecular abnormalities is effective	Exploratory, multicenter, noncomparative trial	Multiple: 30 treatments, both FDA approved and investigational, that target gene abnormalities	Advanced solid tumor, lymphoma, or myeloma; DNA sequencing for actionable mutations	35 adults planned per substudy; pediatric study to begin in 2017	Tumor response (primary) and progression-free survival
B2225	Basket trial to determine cancers responsive to imatinib	Phase 2, multicenter, open-label, noncomparative trial	Single: imatinib (400 or 800 mg per day)	40 cancers (solid tumors and hematologic cancers) with activation of imatinib target kinases	186 patients ≥15 yr of age	Tumor response (SWOG criteria and investigator's assessment)

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

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Woodcock , NEJM 2017

*Examples of Master Protocols in Cancers

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

I-SPY 2 - Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging and Molecular Analysis 2; Lung-MAP - Lung Master Protocol; NSCLC - Non–small-cell lung cancer; HER2 - human epidermal growth factor receptor 2

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Woodcock , NEJM 2017

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Master Protocols

Advantages	Challenges
Increased genomic screening efficiency	Additional time and expertise for such complex trials
Accelerated and streamlined clinical development timeline	Differences in interest of (competitive) partners
Enhanced motivation for patient accrual due to inclusion of a broad range of molecular subtypes (chance to be randomized to usual care is smaller)	Requires collaboration of multiple industry, academic, regulatory and community stakeholders
Flexible objectives: explanatory and confirmatory	

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Renfro 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

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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"

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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?

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CEA Challenges – Specific Issues and Needs for NGT

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

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CEA Challenges – Guiding Questions

Guiding Questions	Considerations
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

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based on: Spackman, Genet Test Mol Bioma 2017

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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

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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.

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*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

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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

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*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)

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Deverka JAMA 2014

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)

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Messner Appl Transl Genom 2016

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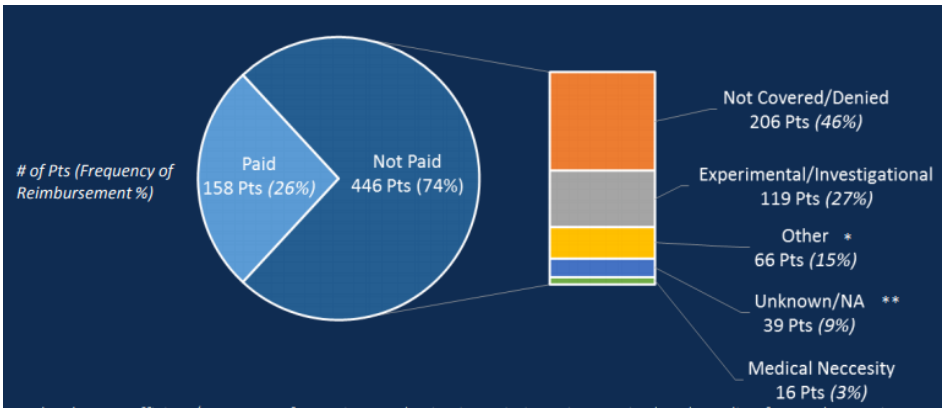
Challenges in Processes: Link HTA - Decision Making

Variation in coverage and reimbursement for a cohort of cancer



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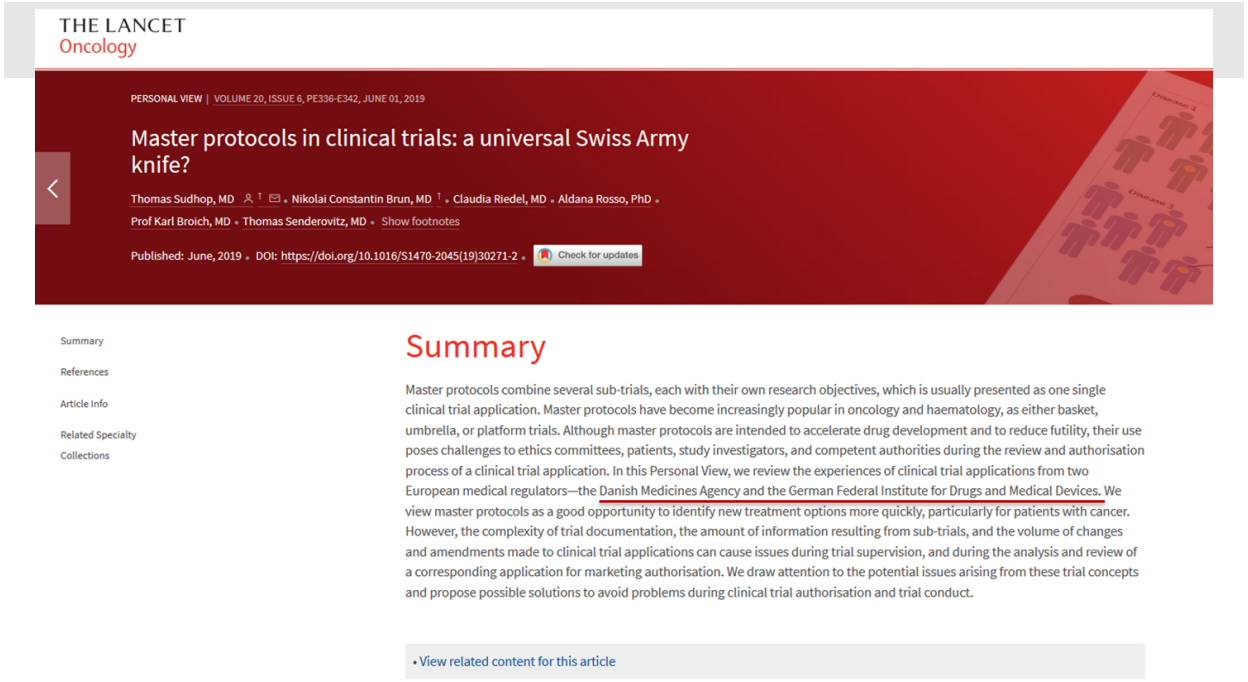
Brown JCO 2017



THE LANCET
Oncology

PERSONAL VIEW | VOLUME 20, ISSUE 6, PE336-E342, JUNE 01, 2019

Master protocols in clinical trials: a universal Swiss Army knife?

Thomas Sudhop, MD • Nikolai Constantin Brun, MD • Claudia Riedel, MD • Aldana Rosso, PhD • Prof Karl Broich, MD • Thomas Senderovitz, MD • Show footnotes

Published: June, 2019 • DOI: https://doi.org/10.1016/S1470-2045(19)30271-2 • Check for updates

Summary
References
Article Info
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Summary

Master protocols combine several sub-trials, each with their own research objectives, which is usually presented as one single clinical trial application. Master protocols have become increasingly popular in oncology and haematology, as either basket, umbrella, or platform trials. Although master protocols are intended to accelerate drug development and to reduce futility, their use poses challenges to ethics committees, patients, study investigators, and competent authorities during the review and authorisation process of a clinical trial application. In this Personal View, we review the experiences of clinical trial applications from two European medical regulators—the Danish Medicines Agency and the German Federal Institute for Drugs and Medical Devices. We view master protocols as a good opportunity to identify new treatment options more quickly, particularly for patients with cancer. However, the complexity of trial documentation, the amount of information resulting from sub-trials, and the volume of changes and amendments made to clinical trial applications can cause issues during trial supervision, and during the analysis and review of a corresponding application for marketing authorisation. We draw attention to the potential issues arising from these trial concepts and propose possible solutions to avoid problems during clinical trial authorisation and trial conduct.

• View related content for this article

Summary

• Challenges for Methods	More complex, methods exists
– Benefit-harm assessment	Master protocols, overdiagnosis
– Cost-effectiveness assessment	Time horizon, downstream consequences, (Dis-)Utilities for knowing?
– Ethical, legal, social issues	Currently poor, values for relatives
• Challenges in Processes	Slow and less predictable
– European regulatory & HTA environment	No common EU pathway, IVD regulation
– Reimbursement process	Currently uncertain, DRGs
– Link from HTA to decision making	Policy barriers, different payer standards

SECTION

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Eric Faulkner
Vice President, Evidera

What Health System Impacts Might Next Generation Testing Deliver?

Are We Ready?

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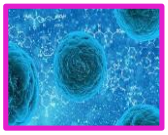
What kinds of health system impacts <u>might</u> we anticipate from the shift towards next generation testing?

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?

	Health System Impact	HTA addresses today?	System incentives exist today for routine consideration?
1	Inform or redefine clinical pathways & improve care equity	?	✗
2	Reduce or avoid the "diagnostic odyssey" in complex disease scenarios	✗	?
3	Dx bridge the continuum of care across the product lifecycle	✗	✗
4	Leverage broader data for integrated care decisions	✗	✗
5	Shape new clinical development models, along w/RWE	?	✓
6	Influence new partnership models around development & access	✗	✓
7	Re-channel limited hospital/health system resources	✗	?
8	Redefine expectations for quality of care, efficiencies and cost flows	?	✓

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1 Inform clinical pathways & improve care equity

Considered now for simpler tests

- Sensitivity & Specificity
- Positive & Negative Predictive Value
- Δ 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?

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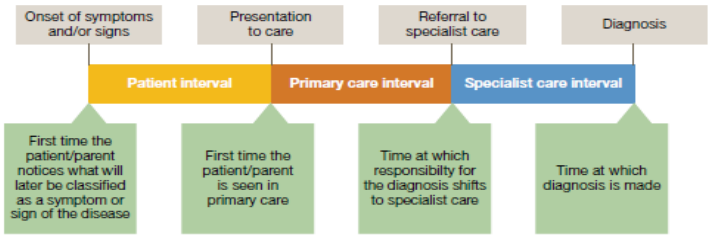
2 Reduce or avoid the "diagnostic odyssey" in complex disease scenarios

Some patients w/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.

Conceptual framework showing Diagnostic Odyssey Inflection Points



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?

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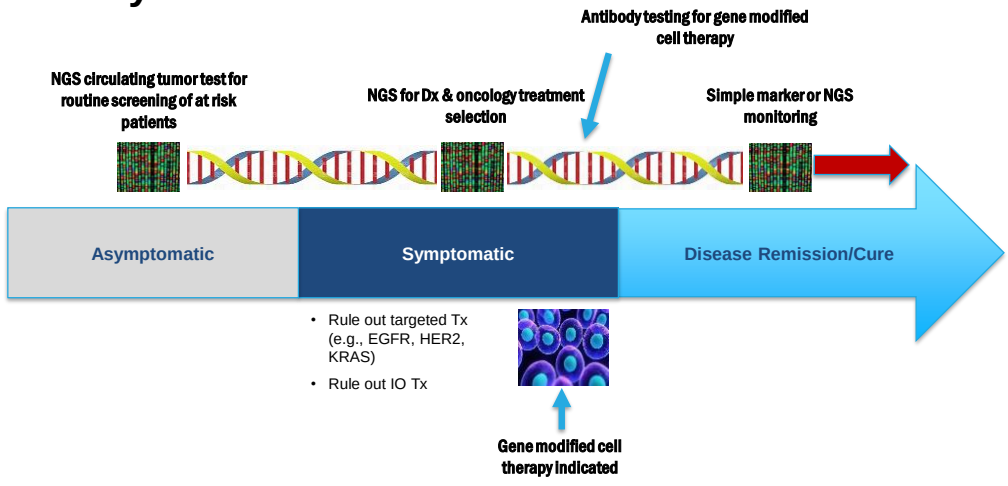
Adapted from Diagnostic odyssey for rare diseases: exploration of potential indicators. Policy Research Innovation Unit. 2015

3 Bridge the continuum of care across the product lifecycle



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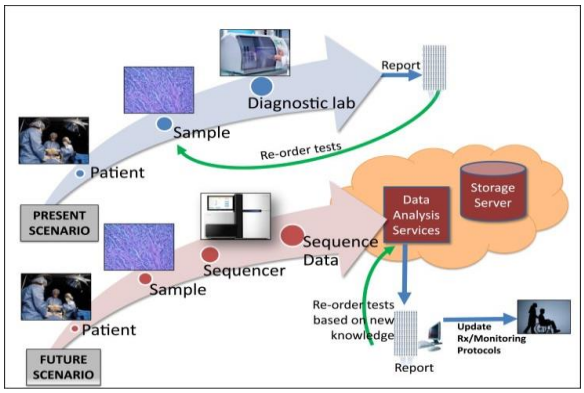
4 Leverage broader integrated data for real-time care decisions (beyond our more 'static' approaches)

Simplified Vision for Future Dx Use



Illustrative clinicogenomics-linked outcomes sources

AI/ Machine Learning

flatiron GRAIL biobank AACR PROJECT GENIE syapse TEMPUS

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?

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Adapted from Kmalakaran S. Translating next generation sequencing to practice: opportunities and necessary steps. Mol Oncol. 2013 Aug; 7(4): 743–755.

5 Shape new clinical development models, along w/RWE

Emerging New Trial Designs

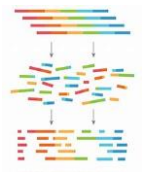
Umbrella Trial

Basket Trial

Adaptive Trial

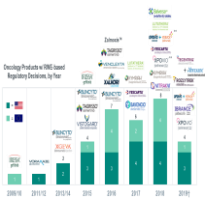
Emerging New Test Approaches & Long-Acting Therapies

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

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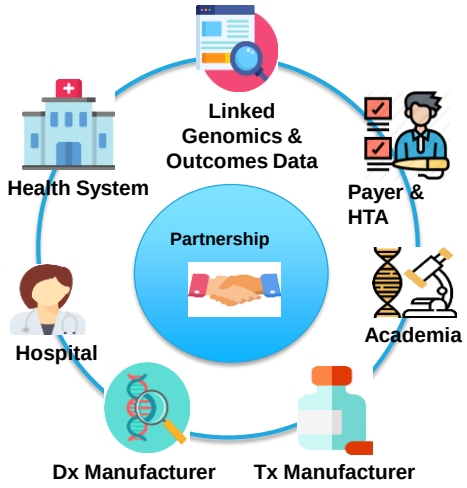
6 Influence new partnership models around development and access



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?

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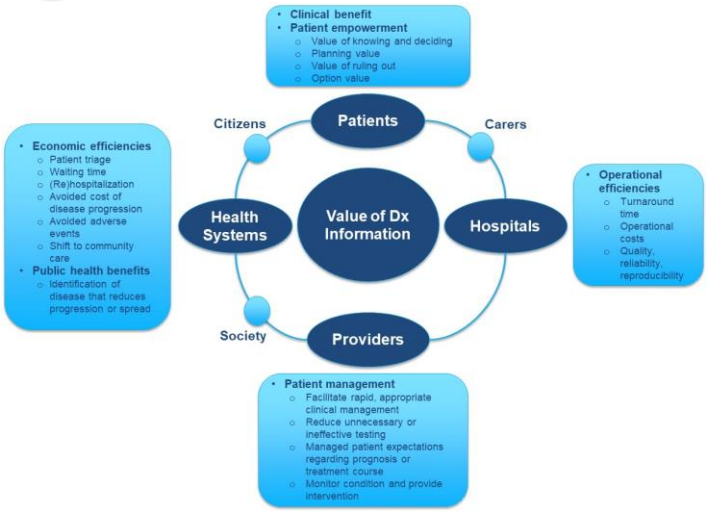
7 Re-channel limited hospital/health system resources



Illustrative Questions

1. What does the value of knowing and/or ruling out offer in terms of **care flow decisions/efficiences**?
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**?

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Adapted from Wurcel et al. The Value of Diagnostic Information in Personalised Healthcare: A Comprehensive Concept to Facilitate Bringing This Technology into Healthcare Systems. Public Health Genomics. 2019;22(1-2):8-15

8 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

Illustrative

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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

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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.**

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