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Improving healthcare decisions

F2: Towards a Value Framework for Precision Medicine: Recommendations from the ISPOR Precision Medicine Special Interest Group

Barcelona, Spain
Monday 12 November 2018

ISPOR Special Interest Group

Speakers

- **Maarten IJzerman, PhD**, Professor and chair Cancer Health Services Research, University of Melbourne, Australia and professor of Health Technology & Services Research, University of Twente, the Netherlands
- **Diana Brixner, PhD, RPh,** Professor, University of Utah, College of Pharmacy, USA
- **Anke-Peggy Holtorf, PhD, MBA,** Managing Director, Health Outcomes Strategies, GmbH, Switzerland
- **Eric Faulkner, MPH,** Vice President, Precision and Transformative Technology Solutions, Value Demonstration, Access and Commercial, Evidera; Assistant Professor, Institute for Pharmacogenomics and Individualized Therapy, University of North Carolina at Chapel Hill, USA

SECTION

1

Maarten IJzerman

Precision Medicine SIG

- To develop good practices for outcomes research in the study design and utilization of genomics involved in personalized/precision medicine.
- Address unclarity about terminology used to describe personalized medicine
- Introduce value-frameworks as a methodological approach to evaluating benefits and harms of precision medicine technologies
- Discuss if existing value-frameworks sufficiently cover value of precision medicine, and value to different stakeholders in particular

Precision Medicine – Changing Paradigms

1. **From "head-to-head" comparisons to "adaptive treatment pathways"**
   - Cost-effectiveness of dynamic treatment sequences instead of head-to-head RCTs
   - Evidence development in precision medicine complicated due *multiple lines* of treatment
2. **Biomarker guided treatment (companion diagnostics / NGS / WGS)**
   - Detailed information about molecular aberrations to find driver mutations
   - Allowing stratification in responder groups, improving efficacy and cost-effectiveness
3. **Liquid-biopsies – circulating biomarkers (ct-DNA, td-EV, CTCs)**
   - Low-cost, minimally invasive, and frequent monitoring of drug response
   - Continuous monitoring of clonal evaluation to guide treatment change
   - Potential health economic return, because of earlier identification of non-response

5

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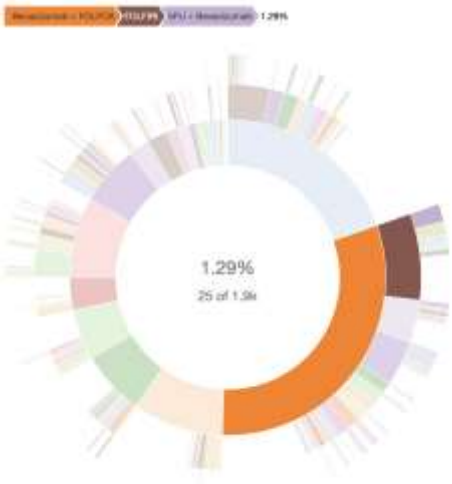
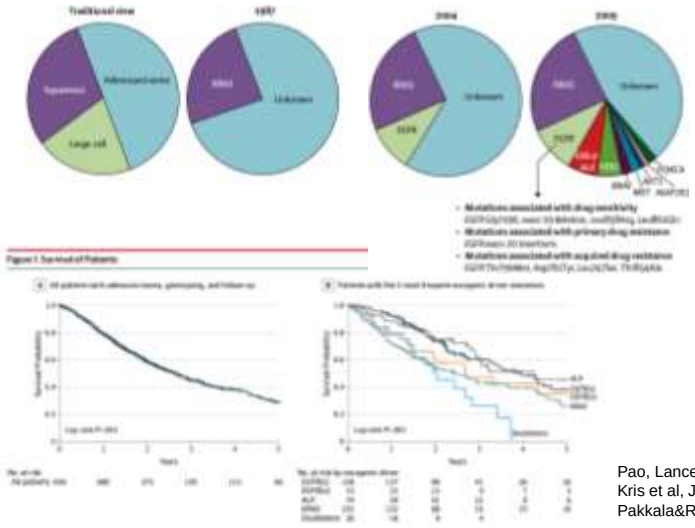
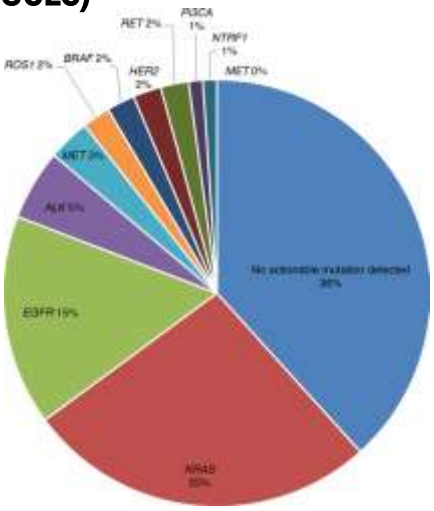
Sunburst of mCRC treatment (TRACC dataset)



Koen Degeling, Hui-Li Wong, Peter Gibbs, Maarten IJzerman

Increase in number of actionable targets (NSCLC)





Pao, Lancet 2011
Kris et al, JAMA 2014
Pakkala&Ramalingam, JCI 2018

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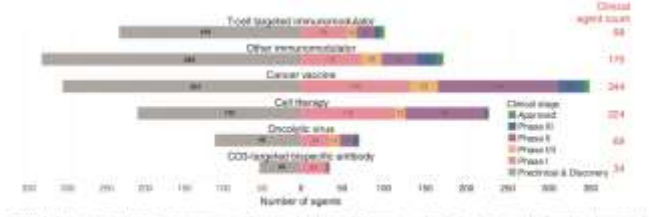
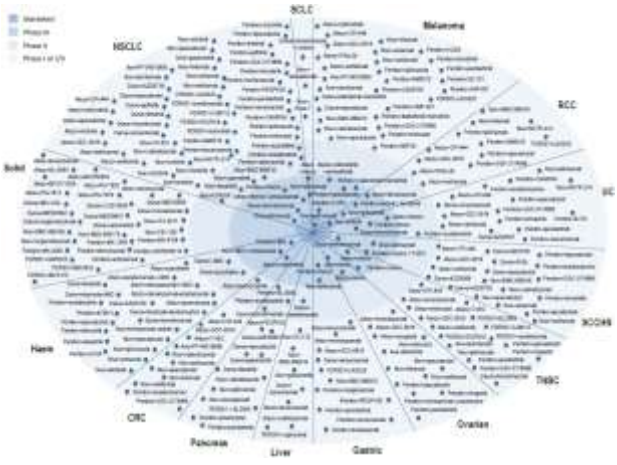
Impressive immuno-oncology pipeline



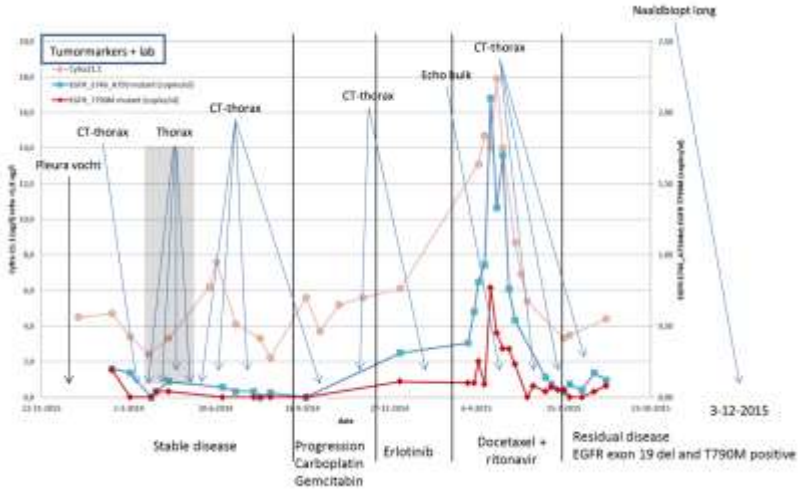
Tang, Shalabi and Hubbard-Lucey, Annals Oncology 2017



"Clinical trials with combination therapies" Chen and Mellman, Nature 2017

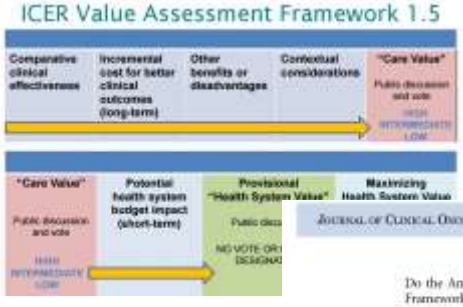
Budget impact of treating all stage IV NSCLC patients in the world with Nivolumab is between 80 – 90 bUS$ (≈ total cancer care budget in Europe)

Liquid biopsies to monitor clonal evolution and non-response



Diagnostic testing strategies for using Nivolumab in NSCLC (N=350) (Daan van den Broek, Huub van Rossum, Mirte Muller, Paul Baas, Michel van de Heuvel)

Value-Frameworks



Questions to the panelists

- Can we present challenges of precision medicine in the EU and US with regard to market authorization and reimbursement?
- Do we need a value-framework for precision medicine applications?
- What value components does a value-framework for precision medicine have to consider?
- How do different stakeholders consider value of precision medicine?

SECTION

2

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Diana Brixner
The Challenges of Defining "Personalized/Precision Medicine"

A Hierarchy of Terms

- ***Personalized Health:*** We are accountable for our own health and make decisions on how we will invest in our health including diet, exercise, lifestyle choices and preventive care
- ***Personalized Medicine:*** Our decisions around our health will often dictate our personal preferences for medicine when we balance effectiveness vs. adverse events
- ***Precision Medicine:*** We introduce diagnostic, biomarkers and imaging to target medicine to optimize outcomes
- ***Individualized Medicine***: Where a specific therapy is only suitable for a single individual based on their unique biochemical makeup

The ability to *assess value* depends on how *value is defined* within each term

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Defining Value in Precision Medicine

- What is the *improvement in outcome* using a particular technology vs. current standard of care where the technology is not used
  - Diagnostic testing to predict the likelihood of a disease occurring
  - Biomarker testing to determine the appropriate therapy (single or panel)
  - Imaging to assess treatment success and further targeting
- What is the *impact on overall cost* of disease management vs. standard of care
  - Onetime diagnostic test to determine preventive strategy to minimize risk vs. treatment of additional incident disease
  - Cost of testing all individuals to only provide expensive therapy where indicated
  - Cost of additional imaging to determine when to stop expensive therapy or continue

The ***value of each technology*** is dependent on its individual impact on outcomes and cost to the patient, payer, provider or society.

SECTION

3

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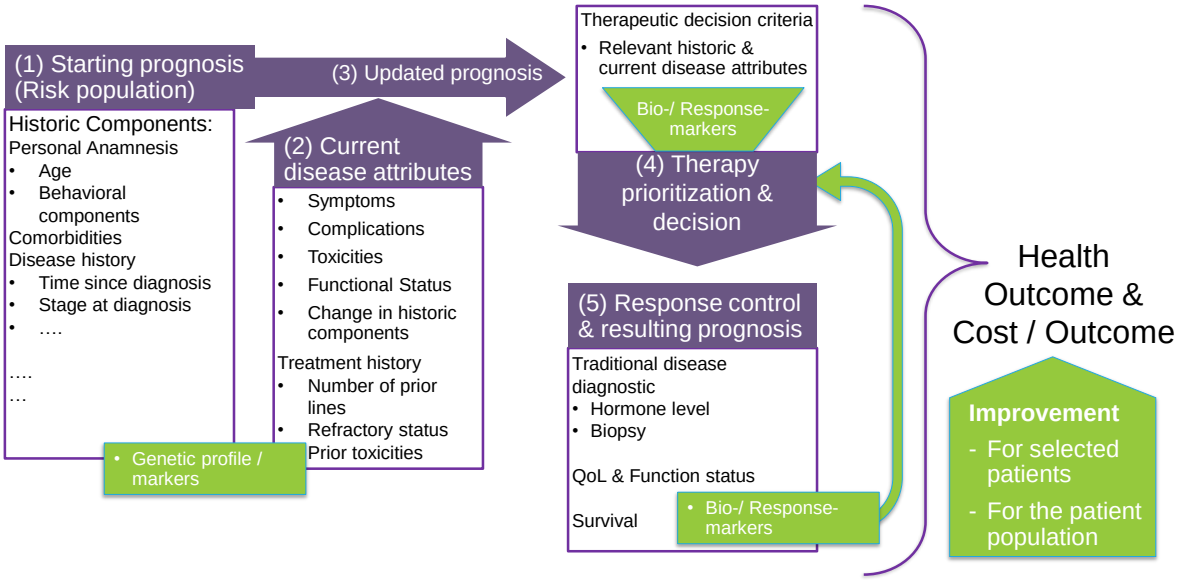
Stakeholder Perspectives on Precision Medicine

Precision … Sounds Expensive

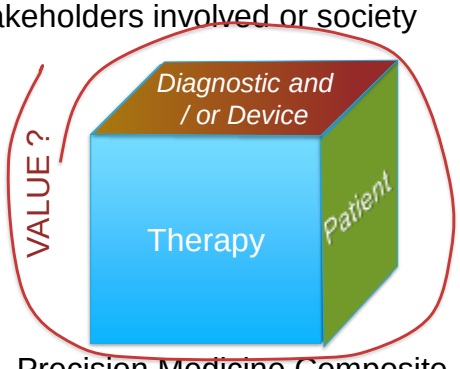
What is Precision Medicine Changing?



Value … to Who?

The benefits, risks, and the costs of healthcare interventions from relevant perspectives of the users, the stakeholders involved or society based on evidence

Single Technology Assessment
- Benefits
- Risks
- Cost
- Ethical Legal Societal Implications



Precision Medicine Composite Assessment
- B / R / C / ELSI of the package or of each component or both?

Who are Those Stakeholders?

- Diagnostic company
- Pharmaceutical company
- The precision positive patient
- The precision negative patient
- Patients with other diseases
- The insurance company (or health fund)
- The provider
- The pharmacist
- The ethicist
- The research community
- The policy maker
- …

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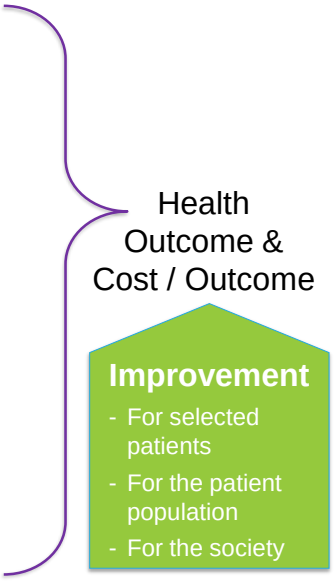
Do All of Those Stakeholders Agree on the Value of Precision Medicine?

- Diagnostic company
- Pharmaceutical company
- The precision positive patient
- The precision negative patient
- Patients with other diseases
- The insurance company (or health fund)
- The provider
- The pharmacist
- The ethicist
- The research community
- The policy maker
- …



Do They Use the Same Measures for Value?

- Diagnostic company
- Pharma company
- The positive patient
- The negative patient
- The other patient
- The insurance fund
- The provider
- The pharmacist
- The ethicist
- The researchers
- The policy maker
- …

Investment	RoI	Margin	Risk	of Dx Component
Investment	RoI	Margin	Risk	of Rx Component
Hope for Health		Fear for restricted Coverage		
No unnecessary side effect		Alternative?		
Insurance cost	Negative impact on my coverage?			
Budget Impact	Savings	Certainty	Fairness	
Efficiency	Reimbursement	Patient Retainment		
Complexity	Shelf Life / Storage	Value Chain		
Societal Impact	Risk	Access	Fairness	
Innovation	Knowledge	Margin	Risk	
Voter impact	Economics	X-National	Fairness	

… Do They Apply the Same Weights?

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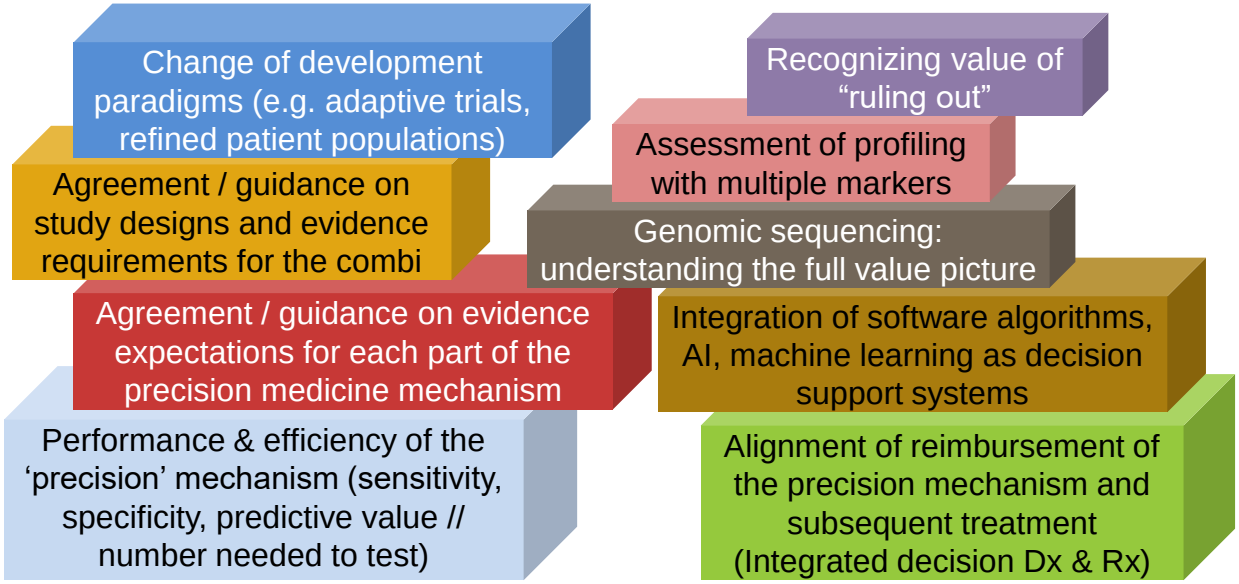
What is the Patient's (or the citizen's) Role in This

- Heterogeneity
- Patient Preferences
- The value of knowing vs. the value of not knowing (Timing)

What Role do Others Play in Precision Medicine, who are agnostic to the healthcare value frameworks ?

- IT World
  - (Precision Algorithms)
  - Surveillance & Risk assessment systems (24/7 measurements)
- Patient Organizations & alikes (23 & me)
- …

Core Components are Required to Make Value Assessment of Precision Medicines Fit



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4

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Eric Faulkner
Vice President, Evidera

Core Components that Value Frameworks Addressing Precision Medicine Should Consider

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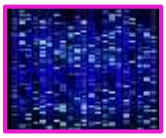
Core Components that Value Frameworks Addressing Precision Medicine Should Consider

1. Incorporating diagnostic performance
2. Alignment of evidence and reimbursement for the test component
3. Clarify acceptable study designs and evidentiary expectations for the test component
4. Clarifying evidence expectations for different diagnostic applications
5. Incorporate value of "ruling out" treatment options



6. Addressing next generation testing special considerations
7. Addressing adaptive trial designs
8. Address potential to target multiple pathways
9. Integration of precision medicine with AI, machine learning & decision support

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1 Incorporating diagnostic test performance into PM HTA

Test Performance

- **Sensitivity** — Ability of test to detect biomarker, even at low levels
- **Specificity** — Ability of test to detect target biomarker
- **Predictive Value** — Likelihood of patient having or not having disease, level of severity, response based on test results
- **Analytic Validity** — Ability of test to detect the intended biomarker

- Test cutoffs influence treatment costs
- False positives & negatives influence treatment costs

Test Impact

- **Clinical Validity** — Ability of test to detect something clinically meaningful
- Δ patient management ← often between
- **Clinical Utility** — Ability of test to improve health outcomes

- Δ patient management influences treatment costs
- Often proxy for clinical utility in mind of some payers

2 Alignment of HTA for test & treatment component

Some agencies review diagnostics separately from associated treatments. Lack of integration can result in challenges…

1

variable and disconnected assessment of the evidence in the context of a companion test & treatment

2

inadvertent patient access limitations if either medicine or Dx is rejected & relationship between the two interventions not acknowledged

Separate processes have resulted in lack of patient access to precision drug when test was rejected…rarely happens today

Now that seem to be moving away from CDx, how will we evaluate?

3

potential to miss nuances in test results/cutoffs that may **impact patient treatment & outcomes**

Initial wave of PD-LI immunotherapies resulted in development of tests w/very different cutoffs – confusing the market & having potential to open patient to risk if tests used interchangeably (later found to be concordant)

4

As next generation testing (e.g., NGS) expands, **potential patient implications become exponentially more complex**

May be difficult w/out modeling or AI to evaluate potential implications of tests w/hundreds to thousands of markers

HOW will HTA handle?

3 Clarify acceptable study designs for the test component

- **No agreement about what "good" or sufficient test evidence looks like** - in practice, a wide range of studies conducted
  - NICE review of EGFR testing illustrates: physician opinion of observational studies
- **Some agencies** developing value frameworks **have taken a stance that test evidence should include RCTs - these proponents ignore the practical & business realities of Dx evidence development**
  - Prior publications have attempted to define a range of non-randomized approaches for addressing key evidence questions associated w/Dx
- **Some agencies** w/ high evidentiary standards (NICE and BlueCross BlueShield Technology Center) **have adopted flexible approaches** vs. other (EUnetHTA) more drug-like approaches
- **Some agencies indicated they do not have experience or time to develop Dx evidence requirements**
- **Establishing clear and consistent "rules of the road" for Dx evidence expectations** is foundational for all health stakeholders

Currently evidence expectations not focused on the questions…

Test Type	Key Questions to Establish Test Value Criteria		
	Analytic Validity	Clinical Validity	Clinical Utility
Screening	•Does the test accurately identify target biomarker or analyte in a large number of well characterized samples (reliability / robustness)?	•Do results correlate with the target condition in an experimental study (few false negatives / high clinical sensitivity, and false positives / high clinical specificity)?	•In the absence of the test, do patients remain undiagnosed or misdiagnosed? •Can results be linked to improved health outcomes in patients with the condition either directly or w/chain of indirect evidence? •Can results be linked to changes in clinical management? •How are at risk populations defined so as to limit unnecessary testing in the broader population?
Treatment Selection Tests	•Is the test sufficiently sensitive to detect the analyte at the required level (few false negatives)?	•Do results correlate with the target condition in the population representing the true asymptomatic condition prevalence (predictive value)?	•Can results be linked to improved health outcomes in patients with the condition either directly or with a chain of indirect evidence? •Can results be linked to change in clinical management? •For what % of tested patients is treatment impacted?
Monitoring	•Is the test sufficiently specific to detect the analyte and nothing else (few false positives)?		•Do monitoring results add incrementally to or result in patient decisions outside of existing SOC approaches? •In the absence of the test, how long does it take for symptoms suggest treatment change? •Can results be linked to change in clinical management? •What are the risks of changing or not changing treatment?

Faulkner E, Spinner D, Ransom J. Developing appropriate evidence for demonstrating the value of diagnostics: where are we now and what is appropriate for the future state? Journal of Managed Care Medicine 2016:19(4):66-78

4 Clarify evidence requirements for different test applications

Evidence Considerations*	Screening / Risk Assessment	Diagnosis	Monitoring	Limitations / Issues
Clinical Lab Research (preclinical validation/ analytical validation)	★ ●	★ ●	★ ●	• More appropriate for analytical validity, especially w/ predicate device
Method Comparison (Prospective)	● ● ●	● ● ●	● ● ●	• More appropriate for CER on tests method
Case Series	N/A	N/A	N/A	• Insufficient
Cross-sectional Study	●	●	N/A	• Can require large sample if rare condition for screening & Dx
Case-control Study (Retrospective)	N/A	N/A	N/A	• Only applicable for biomarker test w/ history of use
Longitudinal Cohort Study (Prospective)	● ●	● ●	● ●	• Can be done as observational
Retrospective Tissue Registry Study	☆	☆	☆	• Limited to already collected samples
Prospective Observational Study	● ★	☆ ★	☆ ★	• Less costly / real world applicability
Naturalistic / Pragmatic Trial	● ●	● ●	● ●	• Can be complex & costly
Randomized Controlled Trial**	● ★	N/A	N/A	• Too complex / costly for most applications

A = Evidence package can include meta-analysis from multiple studies, including from predicate devices
B= Screening only, not risk assessment
C = Arms of RCT for screening test should be test vs. don't test; while arms of RCT for predictive test should be treat vs. don't treat

Sufficient and recommended for (if well-designed):
● = Analytical Validity ★ = Most appropriate evidence approach for analytical validity
● = Clinical Validity ☆ = Most appropriate evidence approach for clinical validity
● = Clinical Utility ★ = Most appropriate evidence approach for clinical utility

- Different test applications can have different evidentiary requirements "dialed" to the specific evidence questions & risk
- E.g.,: significant difference between evidence requirements for screening (high volume/ broad patient risk) vs. monitoring (low volume & focused on ID of disease progression/ treatment failure)
- Globally rules of the road not clearly established

Faulkner E, Spinner D, Ransom J. Developing appropriate evidence for demonstrating the value of diagnostics: where are we now and what is appropriate for the future state? Journal of Managed Care Medicine 2016:19(4):66-78

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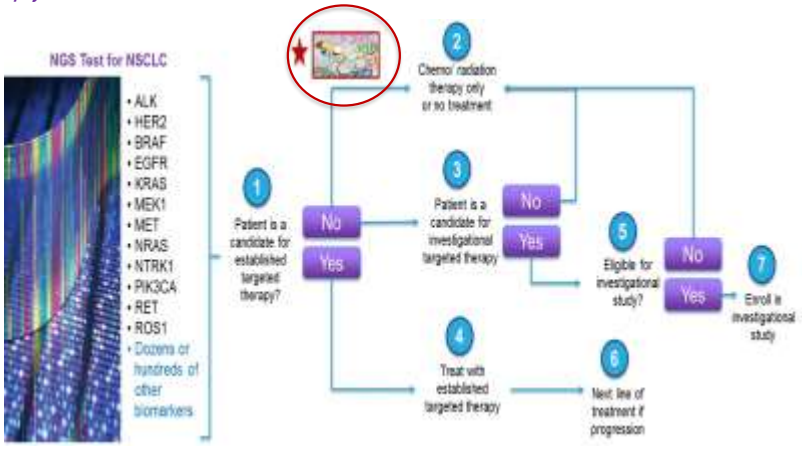
5 Incorporate value of ruling out

Value of using precision medicine for ruling out disease risks or need for certain downstream tests or treatments is often missed by HTA agencies and payers



★ = opportunity for savings and quality vs. non-precision treat all models

- Implications of ruling out certain treatment routes vs. a more trial-n-error approach rarely considered in value assessment
- Further, reflexive NGS testing may evolve as means to establish patient clinical pathway by ruling in/out certain options
- Additional potential for broader savings may flow from increasing decision certainty at time of diagnosis

Alternate example: Troponin testing 98% accurate in ruling out heart attack

6 Addressing next generation testing special considerations

Illustrative Companies

FOUNDATION MEDICINE
nanoString technologies
Knome
Agilent Technologies
illumina
life technologies

NGS brings unprecedented ability to inform decisions beyond current HTA

- Uncertainties around expectations for validation of individual biomarkers in a test or algorithm
- Implications of identifying patient risk factors or diseases not anticipated by the test
- Potential for overuse, harms or ethical considerations flowing using a precision mechanism
- Potential for a test 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 of precision medicine beyond standard clinical or economic metrics

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7 Addressing adaptive trial designs

Our ability to leverage biomarkers is enabling novel trial designs that offer efficiencies vs. traditional test one scenario clinical trials…but they also potentially change the scope & nature of the evidence base available at launch

Umbrella Trial

Subgroups of patients w/same disease treated w/different medicines that target a specific mutation(s)

Basket Trial

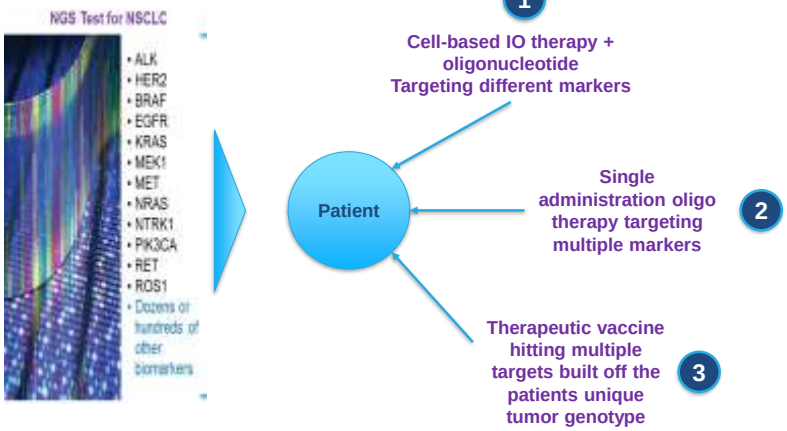
Using same treatment in multiple diseases that have a common mutation target
(e.g., lung, breast, colon cancer)

Adaptive Trial

Study of different subgroups of patients where treatment approach evolves based upon learnings; includes features such as subpopulation enrichment & crossover

7 Addressing novel & adaptive trial designs

As use of multi-marker testing panels in clinical research increases, so does the likelihood that we find small subpopulations of responders to therapies or combinations that might not be detected under normal trial scenarios



- Ability to apply these learnings may alter our perception of what appropriate evidence development looks like
- Such scenarios may further "salami slice" patient subpopulations and alter market access and reimbursement models over time
- RWE data collection and application of decision analytics likely to rise

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8 Address potential to target multiple pathways

Drug targeting now

Future drug targeting

New evidence questions for multi-target therapies…

- What is the right comparator?
- What if new treatment has the potential to replace existing combination therapies or cost significantly less than existing combinations?
- What if new treatment targets marker combinations not addressed by existing agents?
- Are there different safety considerations associated with multi-target therapies?
- Are patients less likely to become refractory vs. alternatives?
- Will such therapies offer greater magnitude or prolonged duration of effect?
- Do such therapies have transformative or curative potential? Does this change value assessment processes and how?

9 Integration of PM with AI, Machine Learning & Decision Support

There are more questions than answers here at the frontier…

- Should AI/machine learning applications driven or strongly influenced/by biomarker data even be considered precision medicine?
- How should these evidence applications be regulated and assessed?
- Where does the line between a product or tool used to actively inform patient interventions begin and end (biomarker-based algorithms vs. population-based decision analytics)?
- Should evaluation be limited to commercial products? Or subscription platforms also?
- What evidence base is relevant? What does "good" look like?
- How and to what extent should such applications be integrated into PM value frameworks if use has profound impact on patient care, outcomes, and resource use?

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