WORKSHOP 7: Are Payers Equipped To Assess The Unique Value Of Precision And Personalized Medicine (PPM)? Analyzing Current Value Frameworks And Their Application Within The PPM Context

Presented by the ISPOR Precision Medicine: Assessing the Value Working Group of the Precision / Personalized Medicine Special Interest Group

Monday, May 22, 2017

ASSESSING THE UNIQUE VALUE OF PRECISION AND PERSONALIZED MEDICINE: ANALYZING CURRENT VALUE FRAMEWORKS AND THEIR APPLICATION

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Personalized/ Precision Medicine Special Interest Group

Goal:
To develop good practices for outcomes research in the study design and utilization of genomics involved in personalized/precision medicine.

Objective:

- Provide a definition of the three key terms used: precision medicine, personalized medicine, and stratified medicine
- Describe the role of health economic and outcomes research (HEOR) in the context of providing an evidence base to support the use of precision medicine
- Identify key research recommendations for applied research and methodological developments to provide an evidence base to support the use of precision medicine

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Precision and Personalized Medicine

Overview

We Are All Zebras

Precision medicine sees the zebra in all of us and focuses not on what makes you part of the herd but what makes you **unique**.

Source: We Are All Zebras: How Rare Disease Is Shaping the Future of Healthcare (https://www.sireninteractive.com/rare-disease-and-precision-medicine-infographic)

How does it work?

Techniques/tools classify patients by sources of variation (e.g., disease subtypes, genomic variation, preferences) and **apply** this **information** to provide **customized treatments** at the individual patient level to those most likely to benefit.

Precision/Personalized Medicine Basic Overview

- **Common Terms** (used interchangeably)
  Precision, Personalized, Stratified, Individualized
- **Purpose**
  - More precisely define diseases using PM tools
  - Stratify treatments, personalize interventions, individualize care
    compared to empirical medicine/therapy based on experience and observation without knowledge of the cause or nature of the disorder

Example: Empirical Medicine vs. Precision Medicine
Infection by an unknown organism is treated with a broad-spectrum antibiotic while awaiting the results of bacterial culture and other tests to identify the organism before providing targeted antibiotic therapy

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Precision Medicine Defined (No formal definition)

The tailoring of medical treatment to the individual **characteristics** of each patient … to classify individuals into subpopulations that differ in their susceptibility to a particular disease or their response to a specific treatment. Preventative or therapeutic interventions can then be concentrated on those who will benefit, sparing expense and side effects for those who will not.

Source: National Research Council, *Toward Precision Medicine* (NRC, 2011).

Biomarker

Objectively measured **characteristic** evaluated as an indicator of normal biological processes, pathogenic processes or pharmacologic responses to a therapeutic intervention. Can be macromolecules (DNA, RNA, proteins lipids), cells, or processes that describe a normal or abnormal biological state in an organism.

Source: IOM, Biomarker Tests for Molecularly Targeted Therapies 2016

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Precision/Personalized Medicine Descriptions

- "Personalized medicine is health care that tailors interventions to individual variation in risk and treatment response." [1]
- "A new paradigm in disease classification, diagnosis and treatment … incorporates and integrates genetic information, microbiome data, and information on patients' environment and lifestyle to better identify and classify disease processes, and to provide custom-tailored therapeutic solutions." [2]
- "Precision Medicine seeks to improve stratification and timing of health care by utilizing biological information and biomarkers on the level of molecular disease pathways, genetics, proteomics and metabolomics "[3]

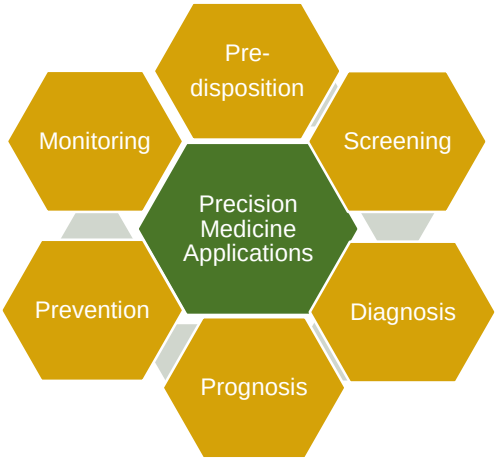
[1] Conti R et al. , Personalized medicine and genomics: challenges and opportunities in assessing effectiveness, cost-effectiveness, and future research priorities. Med Decis Making. 2010 May-Jun;30(3):328-40.
[2]McGrath S and Ghersi D. , "Building towards precision medicine: empowering medical professionals for the next revolution" BMC Med Genomics, 2016: 9:23.2016
[3]Schleidgen et al, "What is personalized medicine: sharpening a vague term based on a systematic literature review," BMC Medical Ethics, Dec 2013, 14:55

PM Tools to Individualize Care

PPM tools are tests or algorithms differentiating

- Responders from non-responders to a specific treatment
- Patients with a good prognosis from patients with a bad prognosis
- People at high risk from those at low risk
- A specific disease state from other ones

Evidence base is needed to inform if, when and how, to incorporate them into clinical practice



Pucheril, D., & Sharma, S. (2011). The History and Future of Personalized Medicine. Managed Care. *http://managedcaremag.com/archives/2011/8/history-and-future-personalized-medicine*

Clinical Uses of Biomarkers

Screening	Detect and treat early stage disease in the asymptomatic population.
Diagnosis/differential diagnosis	Definitively establish the presence and precise description of disease.
Classification	Classify patients by disease subset.
Prognosis	Estimate the risk of or the time to clinical outcomes.
Prediction/treatment stratification	Predict response to particular therapies and choose the drug that is most likely to yield a favorable response in a given patient.
Therapy-related risk management	Identify patients with a high probability of adverse effects of a treatment.
Therapy monitoring	Determine whether a therapy is having the intended effect on a disease and whether adverse effects arise.
Posttreatment monitoring	Provide early detection and treatment of advancing disease or complications.

SOURCES: Adapted from IOM, 2007, 2010a.

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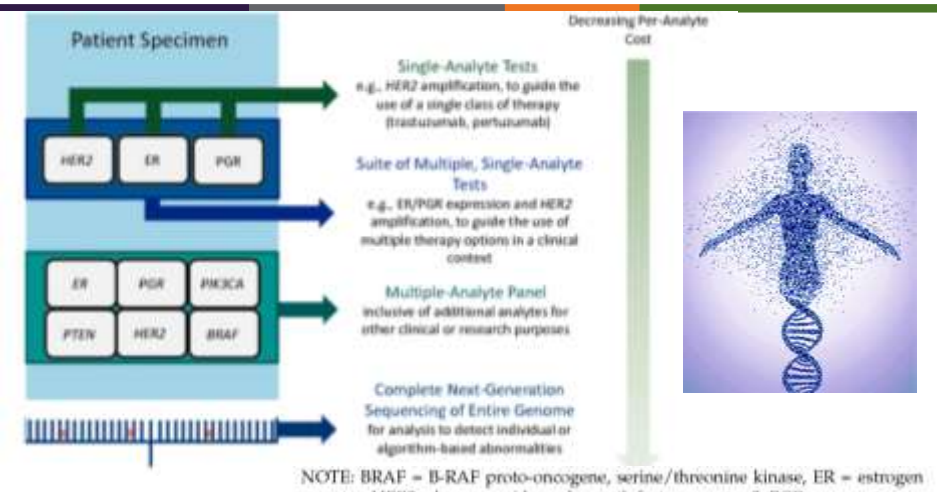
Types of Biomarker Tests



NOTE: BRAF = B-RAF proto-oncogene, serine/threonine kinase, ER = estrogen receptor, HER2 = human epidermal growth factor receptor 2, PGR = progesterone receptor, PIK3CA = phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha, PTEN = phosphatase and tensin homolog; all are analytes potentially detected by biomarker tests in oncology.
SOURCE: Adapted from Yu et al., 2015.

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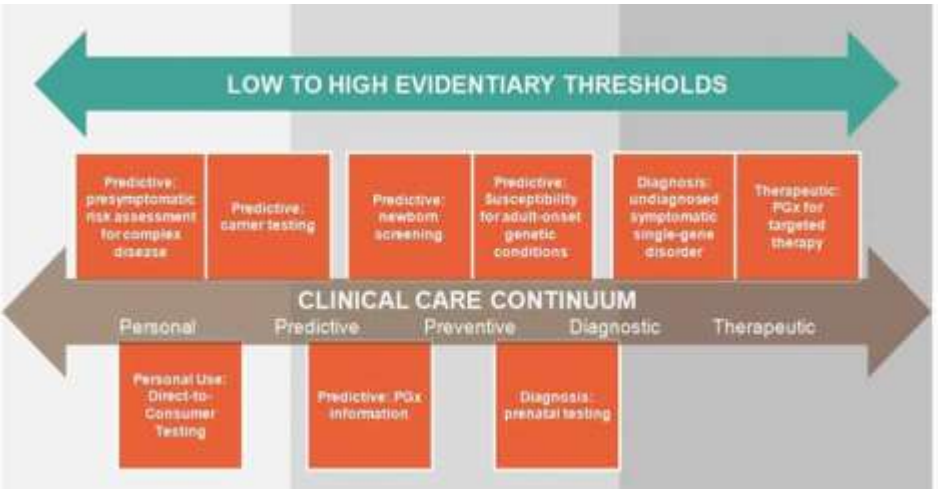
Source: IOM, Biomarker Tests for Molecularly Targeted Therapies 2016

PM Tools: Evidence and Clinical Care



Source: Delaney et al. "Toward clinical genomics in everyday medicine: perspectives and recommendations" Expert Rev Mol Diagn. 2016 May 3; 16(5): 521–532.

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PM Tools

Test type	Purpose description	Example(s)
Diagnostic testing	Precisely identify disease presence and assist in clinical decision-making	Creatine kinase (CK) level testing for Duchenne muscular dystrophy
Prognostic or predictive	Predict likelihood/risk (probability) or time of developing a disease (prognosis) or to benefit from certain therapies (predictive)	*HTT* gene for Huntington disease; *BRCA* genes for breast cancer
Carrier testing	To understand the likelihood of passing a genetic disease to a child	*CFTR* gene testing for cystic fibrosis
Prenatal testing	Identify disease in a fetus	Expanded alpha-fetoprotein (AFP) for risk of neural tube defects

Source: Delaney et al. "Toward clinical genomics in everyday medicine: perspectives and recommendations" Expert Rev Mol Diagn. 2016 May 3; 16(5): 521–532.

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PM Tools (continued)

Test type	Purpose description	Example(s)
Disease screening	Biomarker tests/panels and whole-exome sequencing for detection, prevention and treatment of (asymptomatic) individuals	Familial hypercholesterolemia
Newborn screening	Determine if has a disease known to cause problems in health and development (e.g., rare metabolic conditions)	All states must screen for at least 21 disorders by law, and some states test for 30 or more.
Pharmaco-genomics	Classify to determine safe, suitable or optimal drug therapy and dose	*VKORC1* test for likely response to the anticoagulant warfarin.
Patient experience	Patient-related outcomes such as preferences, understanding, psychosocial and behaviorial impact, healthcare utilization, decisional satisfaction or regret	Improve patient-centered care and healthcare quality.

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PM Unique Data Elements

ACCE Model process for evaluating genetic tests

4 main evaluation criteria

Source: http://www.cdc.gov/genomics/gtesting/ACCE

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PM Policy Issues
Affect All Healthcare Stakeholders' Interests

Discovering and creating → Evaluating (regulatory, policy/decisionmaking) → Using

Source: IOM, Biomarker Tests for Molecularly Targeted Therapies 2016. p. 70.

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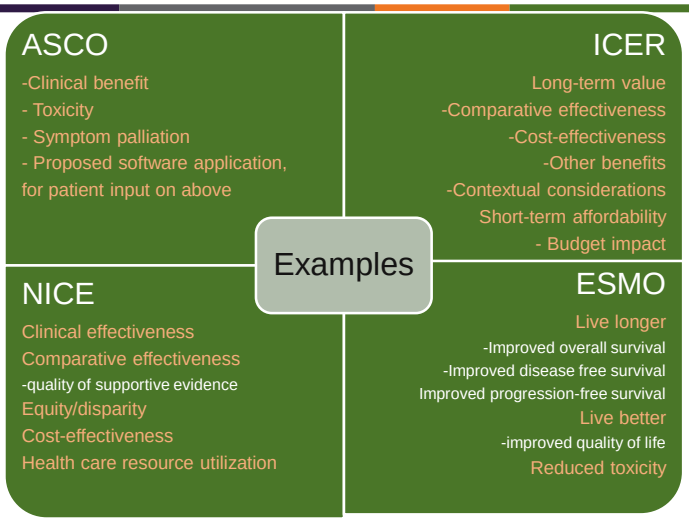
ISPOR Value Assessments of Personalized and Precision Medicine

Purpose of having value frameworks

- Clinical benefit of a new or existing treatment may vary across a wide range
  - small benefit such as few weeks of progression free survival
  - major benefit such as improved long term survival
- Phase III randomized trials are the source of data on efficacy, benefit, and safety of a treatment
- Therefore, a framework is necessary to assess the true magnitude of the clinical benefit offered by the new treatment
  - "breakthrough" or "modest improvement"?
- Frameworks provide a rational, unbiased approach to value assessments, which inform utilization of limited public and personal resources

Elements of existing value frameworks

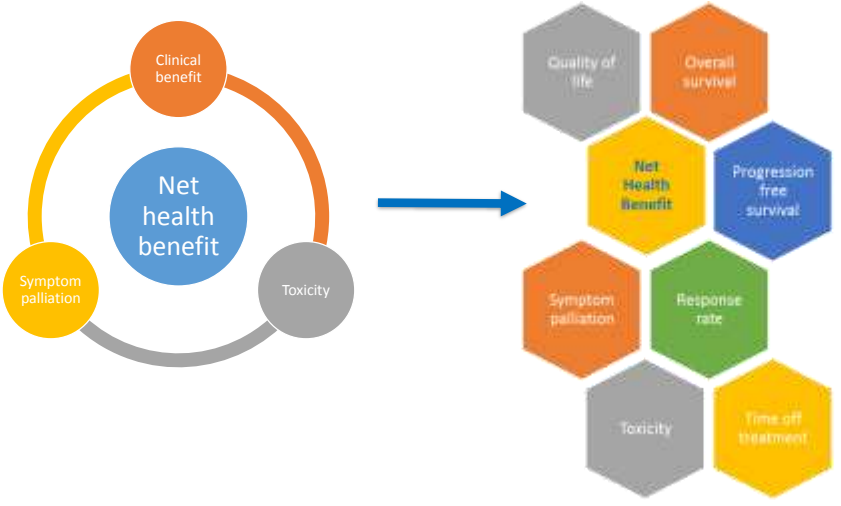


ASCO: American Society of Clinical Oncology; ESMO: European Society for Medical Oncology
ICER: Institute for Clinical Effectiveness and Research;
NICE National Institute of Clinical Excellence

Objectives of the ASCO framework

- To develop a framework that would help assess value of cancer treatment given a patient's preference and circumstances
  - Define value of cancer treatment
  - Support physician- patient discussions on best course of action
  - Capture disease state – advanced or adjuvant

Key features of the ASCO framework (Net Health Benefit)



Strengths of the ASCO framework

- Use of hazard ratios to assess relative efficacy (instead of median overall survival or progression free survival)
- Uses bonus points to capture importance of improved survival and progression free survival
- Includes all adverse events and not just the most severe

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Limitations of the ASCO framework

- Focus solely on cost of prescription drugs
  - Ignores other significant expenditures associated with cancer care
- Lack of Patient Reported Outcomes (PROs), and impact on quality of life
  - Scarce evidence base
  - Potential of being included in future revisions to the framework
- Allows only head to head comparisons

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Objectives of the ESMO framework

- To assess the relative benefit of treatments using the following:
  - Outcomes of survival or quality of life
  - Surrogates for survival or quality of life
    - Disease free interval
    - Event free survival
    - Time to recurrence
    - Progression free survival
    - Time to progression

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Key features of the ESMO Framework (ESMO Magnitude of Clinical Benefit Scale)

- Form 1: used for adjuvant and neoadjuvant therapies with a curative intent
- Form 2: used for agents that are focused on disease management without a curative intent
  - Form 2a: where overall survival is the primary outcome
  - Form 2b: where progression free survival is the primary outcome
  - Form 2c: for therapies being evaluated for non-inferiority or equivalence

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Strengths of the ESMO framework

- Objective, reproducible
- Allows comparison of magnitude of benefits
  - E.g., Overall survival, progression-free survival, quality of life
- Clinically relevant, unbiased criteria
- Wide application, over a range of disease types and stages
- Transparent, reliable and valid development process, open for peer review

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Limitations of the ESMO framework

- Can be applied only in comparative research outcomes – not on evidence from single arm studies
- Sensitive to quality and design of the study
  - Control arm: a weak control arm may lead to an perception of exaggerated benefit
  - Cross over studies: may lead to underestimation of the true benefit of new treatment

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Discussion

- Existing frameworks:
  - Do have some robust features that fit well with all treatments and diagnostic technologies
  - Common themes that cover some of the fundamental concepts of value assessments
- However, with a rapidly evolving landscape of technologies:
  - Perhaps too formulaic, especially when viewed within the context of PPM
  - Overly dependent on trials, without much input from patients and their unique needs
  - Relatively inflexible to accommodate newer technologies

"Impersonal frameworks for personalized treatments…?"

Sources

- https://www.nice.org.uk/About/What-we-do/Our-Programmes/NICE-guidance/NICE-technology-appraisal-guidance (accessed May 9, 2017)
- Cherny, Nathan I., et al. "A standardised, generic, validated approach to stratify the magnitude of clinical benefit that can be anticipated from anti-cancer therapies: the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS)." *Annals of Oncology* (2015): mdv249.
- Schnipper, Lowell E., et al. "Updating the American Society of Clinical Oncology value framework: Revisions and reflections in response to comments received." *Journal of Clinical Oncology* 34.24 (2016): 2925-2934.
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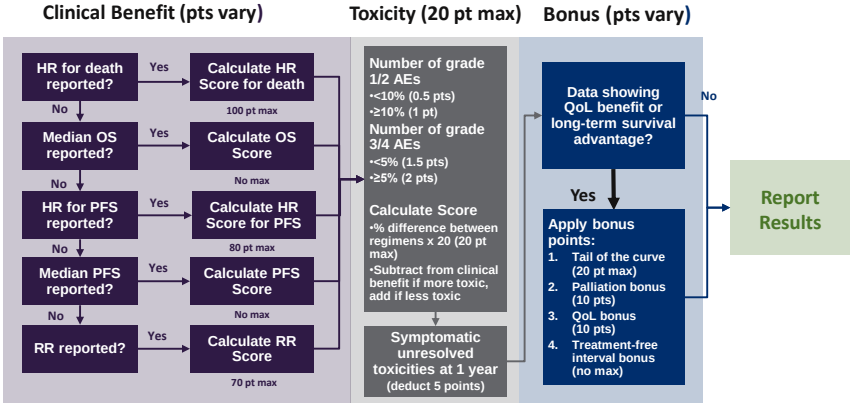
Evaluation of Personalized Medicine in Breast Cancer Against the ASCO Value Framework

ASCO Value Framework: Summary



AE = adverse event; OS = overall survival; PFS = progression-free survival; RR = response rate.

- Schematic based on Schnipper LE, et al. *J Clin Oncol.* 2016;10.1200/JCO.2016.68.2518.

ASCO Value Framework for Advanced Disease

Daratumumab: relapsed patients with multiple myeloma who have received at least three prior lines of therapy, including a proteasome inhibitor (PI)				
Step 1: Determine CLINICAL BENEFIT Assign a PFS Score				
Progression-Free Survival	Assign PFS Score			PFS Score
Step 2: Determine the regimen's TOXICITY: Compare the number of Grade 3-5 toxicities				
Calculate the Toxicity Score	Toxicity Score			Toxicity Score
Step 3: Determine BONUS POINTS				
Palliation Bonus	Significant improvement in cancer related symptoms			Palliation Points
Treatment Free Interval Bonus	Statistically significant improvement in treatment free			Treatment Free Interval Bonus Points
Step 4: Determine the regimen's NET HEALTH BENEFIT				
Step 5: Determine the regimen's COST				Cost per Month: Patient Copay:

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ASCO Value Framework for Advanced Disease

- Clinical benefit points based on outcome measure used!!

Drug	HR OS	Median OS	HR PFS	Median PFS	Response Rate
Carfilzomib	**21.0**	**NR**	**24.8**	**39.5**	**61.0**
Daratumumab*	**23.0**	**NR**	**48.8**	**NR**	**58.0**
Elotuzumab	**NR**	**NR**	**24.0**	**24.2**	**55.3**
Ixazomib	**NR**	**NR**	**20.8**	**32.1**	**54.6**
Panobinostat	**13.0**	**10.7**	**29.6**	**38.7**	**42.5**
Pomalidomide	**26.0**	**56.8**	**41.6**	**88.4**	**21.7**

- The outcome measure used for clinical benefit can make a significant difference
  - Best (green) and worst (red) scores indicate a lack of consistency in metrics across and within products

*Daratumumab based on phase 3 RCT with BORT/DEX instead of single-arm phase 2 study in PI.
Scores calculated based on Schnipper LE, et al. *J Clin Oncol.* 2016;10.1200/JCO.2016.68.2518.

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Personalized Medicine Tool for Evaluation: Multigene Test to Extend Life in Women with Hereditary Breast Cancer

- Seven gene test including TP53, PTEN, CDH1, STK11 and PALB2, along with BRCA 1 and 2 vs. BRCA 1 and 2 alone
- Tested in 40 year and 50 year old cohorts
- Assumed that women identified with pathogenic variants would undergo prophylactic surgery or enhanced surveillance
- Seven gene test vs. 2 gene test:
  - $69,920 per QALY in 50 year old group
  - $48,328 per QALY in 40 year old group

Li Y, Arellano AR, Bare LA, Bender RA, Strom CM, Devlin JJ. A Multigene Test Could Cost-Effectively Help Extend Life Expectancy for Women at Risk of Hereditary Breast Cancer. Value Health. 2017 Apr;20(4):547-555.

Potential Solutions to Define each Attribute FOR Breast Cancer MGT

Attributes	
ASCO	MGT
1.Clinical Benefit	What's the proportion of prevented breast and/or ovarian cancer by using the new test? (TP+TN)
2.Toxicity	False positive rate: unnecessary surgery or surveillance False negative rate; cancer occurrence Variants of Unknown Significance rate; uncertainty
3.Bonus Points	
Palliation	Does the new test request less tissue or short analyzing time?
QoL	Does the patient report higher QoL of receiving the new test?
Treatment Free	N/A (Measured in clinical benefit).
4.Net Health Benefit	The accumulated score of 1 to 3 (Clinical Benefit-Toxicity+Bonus Points).
5.Regimen Cost	Include the test acquisition cost and patient co-pay

Gaps in Applying ASCO Value Framework to Personalized Medicine

- How can stakeholders vary parameters to minimize total cost of care while ensuring optimal outcomes?
- Define outcomes
  - What are the most important outcomes, clinical and economic?
- Weight attributes
  - How much value should be assigned to palliation and patient-reported outcomes?
- Concerns from providers
  - Should providers demand access to pathways (i.e., integrated into electronic medical record [EMR]) for real-time for decision support?)
  - Should providers be allowed to develop their own pathways (as recommended by ASCO)?
- Concerns from patients
  - Should participation be mandatory? What are the incentives for participation and adherence? What are the consequences of selecting an "off-pathway" therapy?

Potential Modifications to ASCO Framework for Personalized Medicine

- With increased focus on value and accountable care, pathways-based initiatives provide an evidence-based tool for managing appropriate utilization in a high-cost therapeutic space
- Request the accuracy of genomic testing from different labs
- Adjust the pathways-based initiatives to a general value, rate, including TP, TN, FP, FN and VUS rate.

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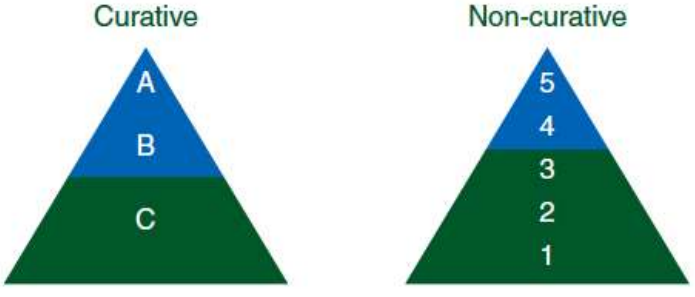
Evaluation of Personalized Medicine in Non-Small Cell Lung Cancer Against the ESMO Value Framework

European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) Framework

ESMO MCBS evaluation



Curative-Evaluation form 1: for new approaches to adjuvant therapy or new potentially curative therapies

Non-curative-Evaluation forms 2a, b or c: for therapies that are not likely to be curative

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The ESMO Framework

- Form 1: evaluate adjuvant and other treatments <u>with curative intent</u>
- Form 2: evaluate treatments <u>without curative intent</u>
  - Form 2a: studies with OS as the primary outcome
  - Form 2b: studies with progression free survival (PFS) or time to progression (TTP) as primary outcomes
  - Form 2c: studies with QoL, toxicity or response rate (RR) as primary outcomes and for non-inferiority studies

- Underlying principles:
  - Cure takes precedence over deferral of death
  - Direct endpoints such as survival and QoL take precedence over surrogates such as PFS
  - Disease free survival in curative disease is a more valid surrogate than PFS (or RR) in non-curative disease
  - Interpretation of the evidence for benefit derived from surrogate outcomes (such as PFS) may be influenced by secondary outcome data

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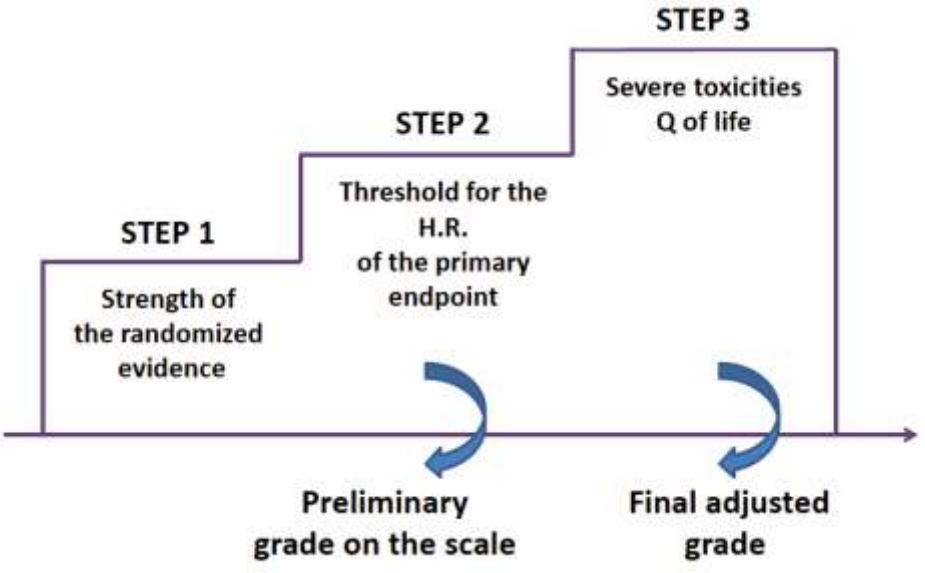
3 Steps for Using the ESMO Framework



Next-generation sequencing in NSCLC patients

- Next-generation sequencing (NGS) can be used to identify multiple specific mutations in a tumor, and inform selection of targeted therapy.
- NGS and targeted therapy can improve patient survival and can reduce unnecessary harms and costs by preventing sequential single-gene testing and ineffective treatments
- Mostly recommended for patients in an advanced stage of disease (i.e., for stage-IV non-small-cell lung cancer (NSCLC)).
- NGS can be very beneficial due to their heterogeneous nature, high mutation frequency, and the availability of targeted therapies.
- Patients with stage-IV NSCLC have a 5-year survival rate of 1%
- In 78% of the NSCLC patients, there are no actionable mutations, and usual chemotherapy or immunotherapy is recommended

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Next-generation sequencing in NSCLC patients

- Nationwide stage IV NSCLC patients in the Netherlands
- Budget impact analysis, including costs for personnel, material, equipment
- Strategies compared & findings:

	Utilization	Costs per patient	Difference in costs
Old (2012)	70% use 1 single-gene test 30% use 3 single-gene test	537 euro	-
Current (2015)	70% use 2 single-gene test 30% use small TGP & 3 single-gene test	864	+327
Future	70% use small TGP 30% use WGS	754	-110

Van Amerongen R, et al. ecancer 2016;10:684
TGP = targeted gene panel

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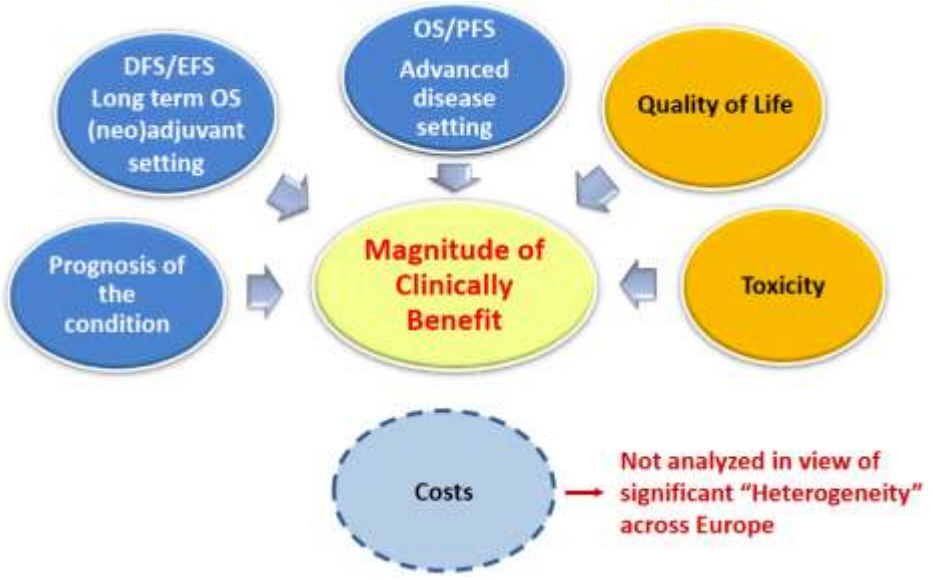
How to define attributes in ESMO framework for NGS for NSCLC?



Considerations for applying value framework to Personalized Medicine

- Identification of mutations does not necessarily translate into the use of a targeted therapy (i.e., not all mutations are clinically actionable)
- Compare test and treat regimes? For example,
  - Multi-gene testing + use of targeted therapies only in patients with clinically actionable alterations;
  - No further testing + treatment with chemotherapy; and
  - No further testing + treatment with best supportive care

  Doble B et al, Lung cancer 2017;107:22-35
- Stage of disease and treatment history.
  - Multi-gene testing can be performed at initial diagnosis to inform use of first-line treatments
  - As treatments are exhausted or on development of resistance to targeted therapies, testing may be used to inform 3rd/4th line treatment

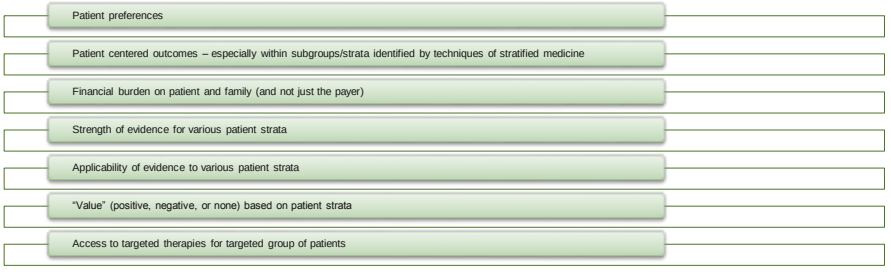
Audience Response Questions for Panel

- Which areas presents the largest challenge to apply to personalized medicine?
  - How to define outcomes?
  - How to assign weights to different attributes?
  - Concerns from providers
    - What's the optimal pathway?
    - Could providers adjust it?
  - Concerns from patients
    - Should participation be mandatory?
    - What are the incentives for participation and adherence?
    - What are the consequences of selecting an "off-pathway" therapy?
- Other concerns/suggestion? Open Discussion

Audience Response Questions for Panel

- Audience Perspectives
  - Industry;
  - Academia;
  - Patient/patient advocacy group;
  - Payer
  - Other
- Which area works best for personalized medicine
  - How to define outcomes?
  - How to assign weights to different attributes?
  - Concerns from providers
    - What's the optimal pathway?
    - Could providers adjust it?
  - Concerns from patients
    - Should participation be mandatory?
    - What are the incentives for participation and adherence?
    - What are the consequences of selecting an "off-pathway" therapy

Elements to consider in a PPM value framework



Current initiatives

- Avalere Patient Perspective Value Framework (PPVF)

http://avalere.com/expertise/life-sciences/insights/releasing-the-draft-avalere-fastercures-patient-perspective-value-framework

Sign up as Review Group Member

- Sign up as Review Group Member
- Join ISPOR Special Interest Groups
- Need ISPOR membership number
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