Health Technology Assessment Research and Precision Medicine

EULAC PerMed 2nd Summer School

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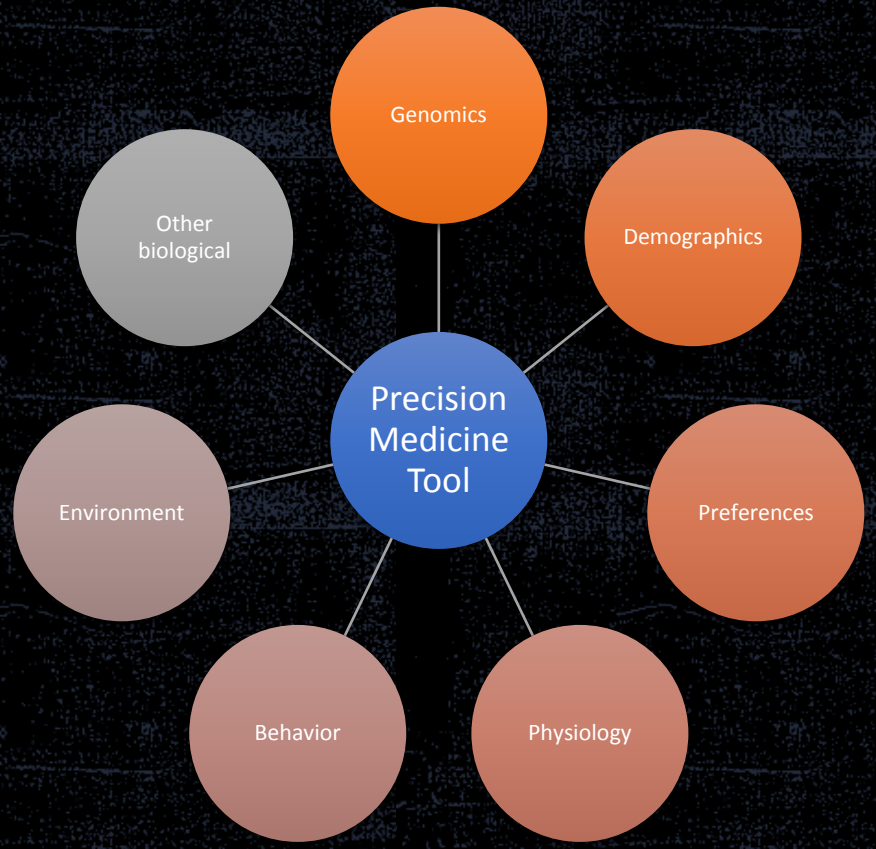
Disclaimer

- I provide advisory support and consultancy for:
  - ISPOR
  - AMGEN
  - P4H – Partners for Health Partnership
  - European Commission

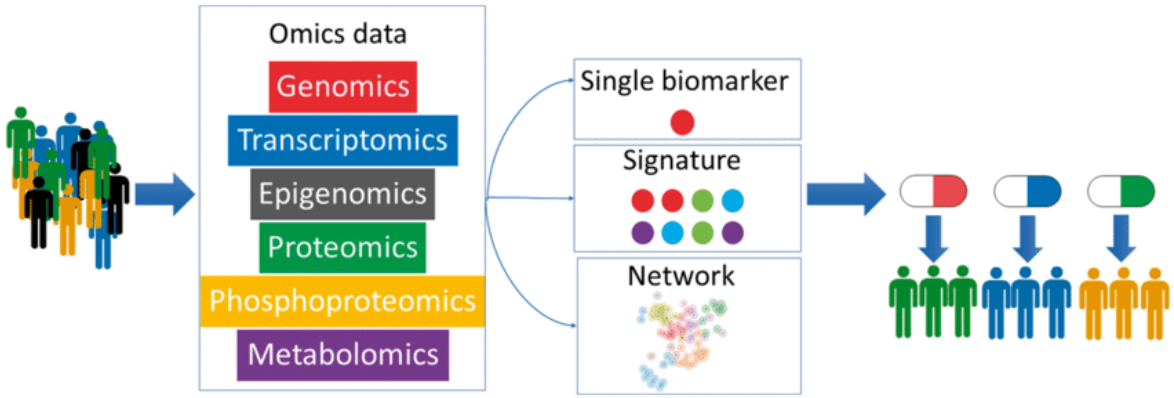


Disease susceptibility
Diagnosis
Prognosis
Treatment response

Love-koh, J. PharmacoEconomics (2018) 36:1439–1451

‘Omics’-based testing is expected to increase in complexity and scope, with single tests informing treatment pathway, therapy choice or disease risk for multiple diseases simultaneously.
Whole-genome sequencing is at the broadest end of this scale and could feasibly provide information on risks and treatment decisions for hundreds of diseases

#precisionmedicine



Source: Manuel Cossio, MSc (https://www.linkedin.com/in/manuel-cossio-36043759/)

Digital biomarkers in diseases

Fertility

Ava tracker

Ovulation time
Accelerometer (movement/sleep)
Temperature sensors
Skin conductance
Blood circulation

Asthma/ COPD

Propeller sensor

Frequency of rescue inhaler use
Air App: Pollution, Pollen, Humidity, Temperature

Heart disease

AliveCor Kardia
(FDA approved)

ECG
Heart rate
Sinus rhythm

Depression

Mindstrong

Human-computer interactions
Voice analysis
Activity, location, social meta-data

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Current Health Technology Assessment (HTA) Landscape

Current approaches to economic evaluation to support decision making are largely focused on reimbursement of drugs.

Drug reimbursement evaluations are typically population based, involving single interventions in single populations.

Because personalized medicine (PM), by definition, leads to restricted populations or individual care there are questions as to whether current approaches to economic evaluation are adequate for PM interventions.

HTA agencies' experience of PM has primarily been with diagnostic and companion diagnostic tests (those that identify biomarkers correlated with treatment response such as the HER2 receptor protein for breast cancer)

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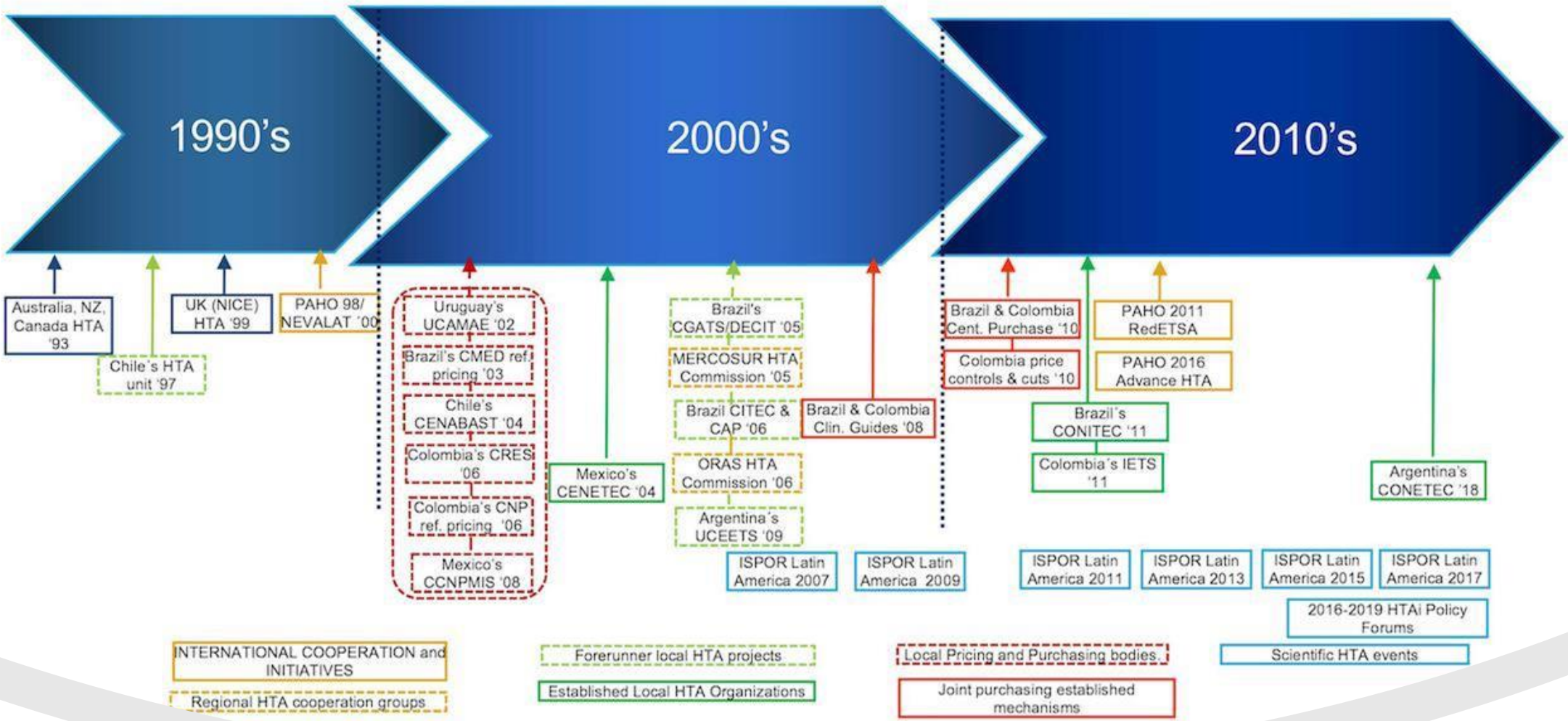
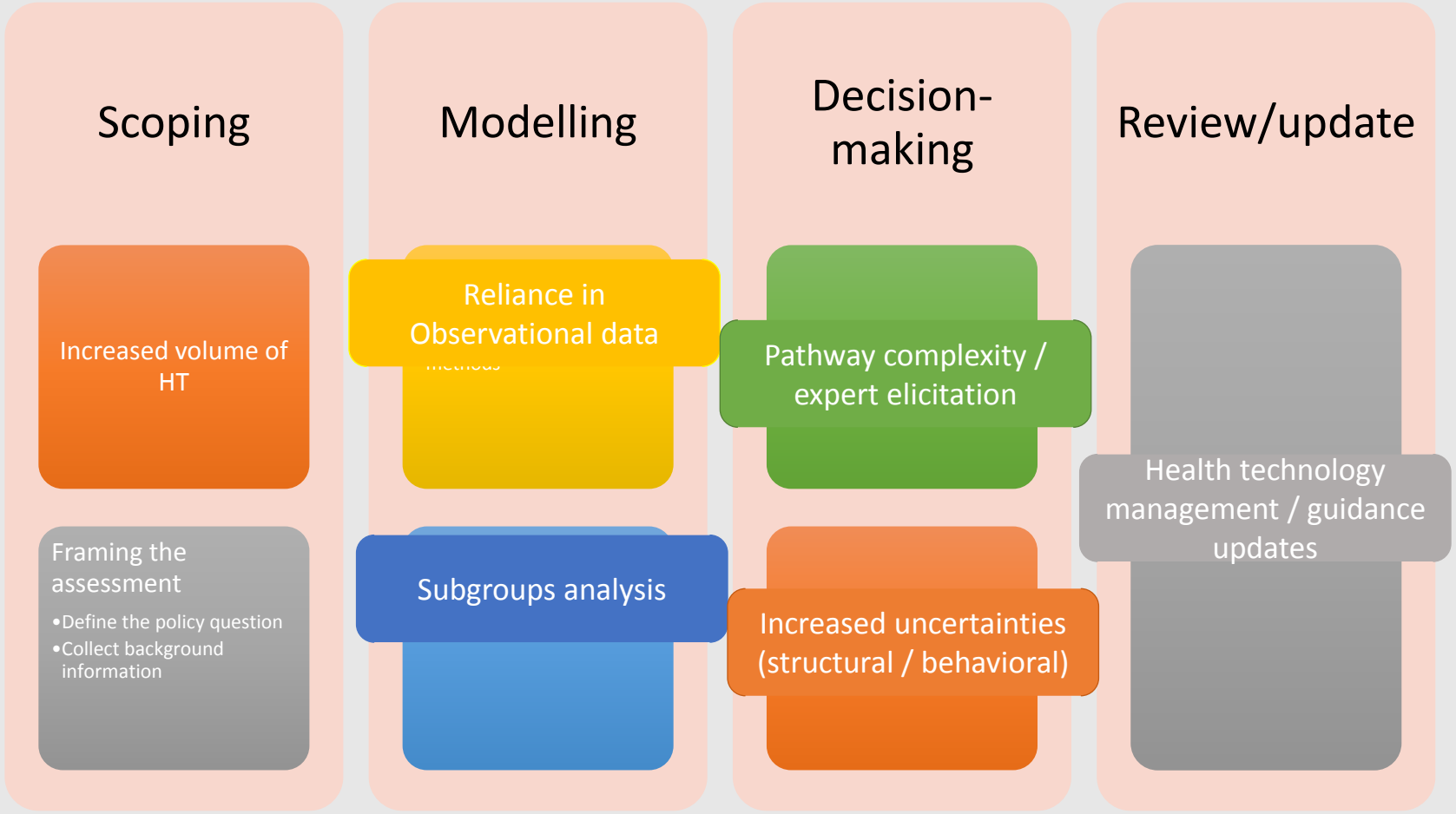


Gilardino et al, 2019

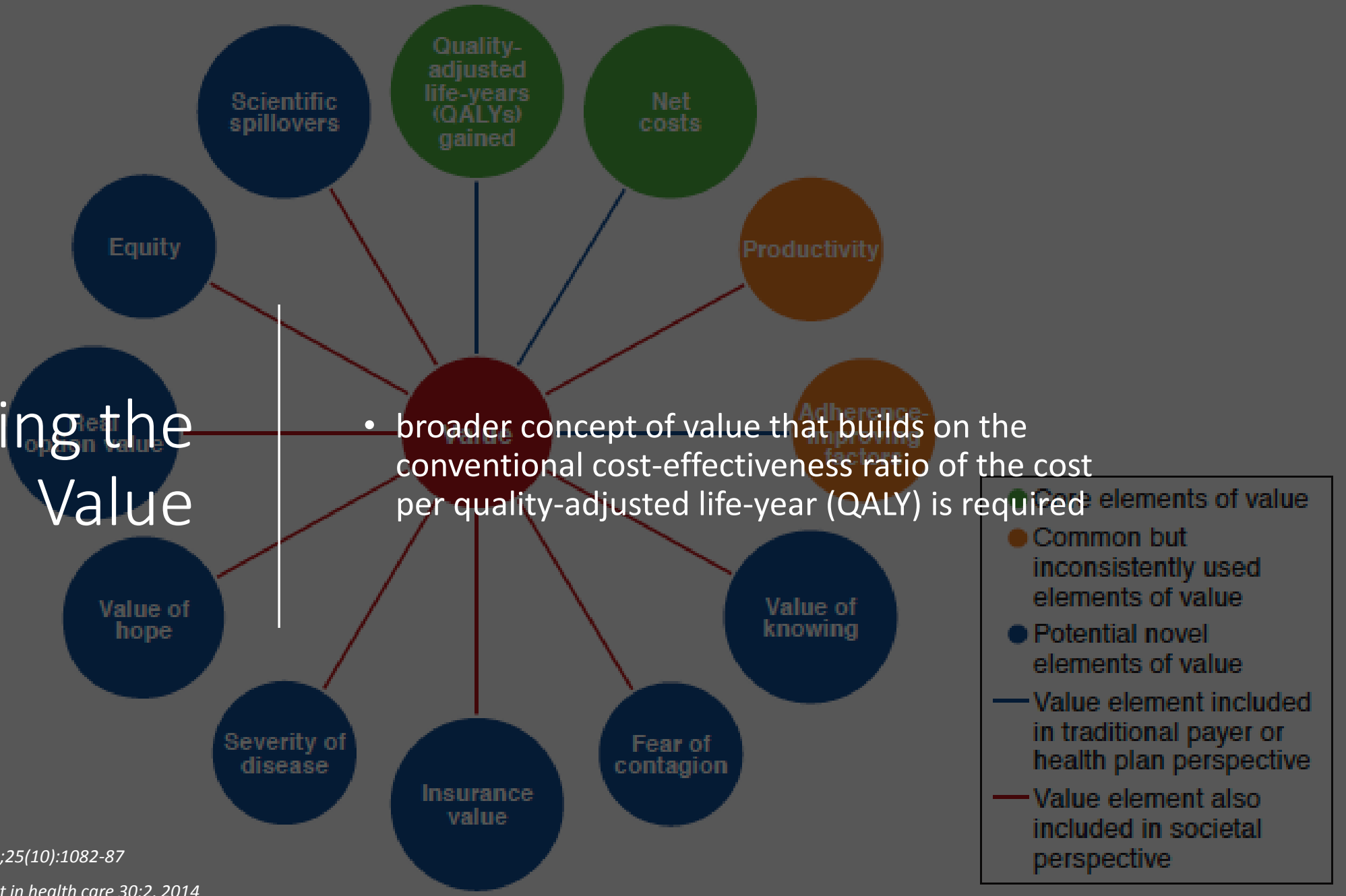
Defining the HTA process



Love-koh, J. PharmacoEconomics (2018) 36:1439–1451

Measuring the Value

- broader concept of value that builds on the conventional cost-effectiveness ratio of the cost per quality-adjusted life-year (QALY) is required



Garrison L. . J Manag Care Spec Pharm. 2019;25(10):1082-87

Husereau, D. Intl. J. of technology assessment in health care 30:2, 2014

Adapted from: Lakdawalla DN, Doshi JA, Garrison LP Jr, Phelps CE, Basu A, Danzon PM. Defining elements of value in health care—a health economics approach: an

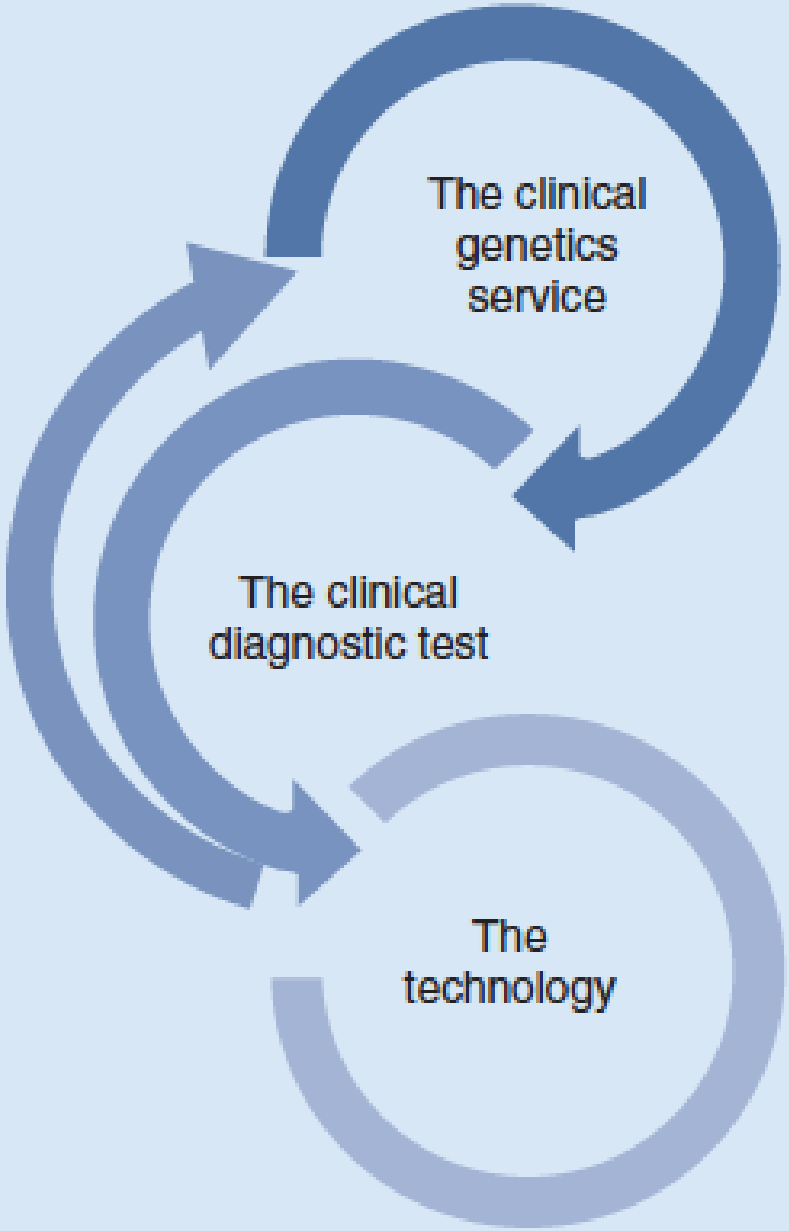
Assessing the evidence

P	Patient, Population, or Problem	How would I describe a group of patients similar to mine?
I	Intervention, Prognostic Factor, or Exposure	Which main intervention, prognostic factor, or exposure am I considering?
C	Comparison to Intervention (if appropriate)	What is the main alternative to compare with the intervention?
O	Outcome you would like to measure or achieve	What can I hope to accomplish, measure, improve or affect?
T	**What type of question are you asking?**	**Therapy/Treatment, Diagnosis, Prognosis, Harm/Etiology** (may be referred to as "**domains**" in PubMed)
T	**Type of study you want to find**	**What would be the best study design/methodology?**

Assessing the evidence

- Testing reveals heterogeneity and creates multiple subpopulations which unfold according to the sequence information is gathered.
- Sample size reduction due to small patient subgroups.
- Obtaining head-to head estimates of comparative effectiveness for treatments and subgroups will become more difficult
- Increasing role in the expert opinion

Love-koh, J. PharmacoEconomics (2018) 36:1439–1451

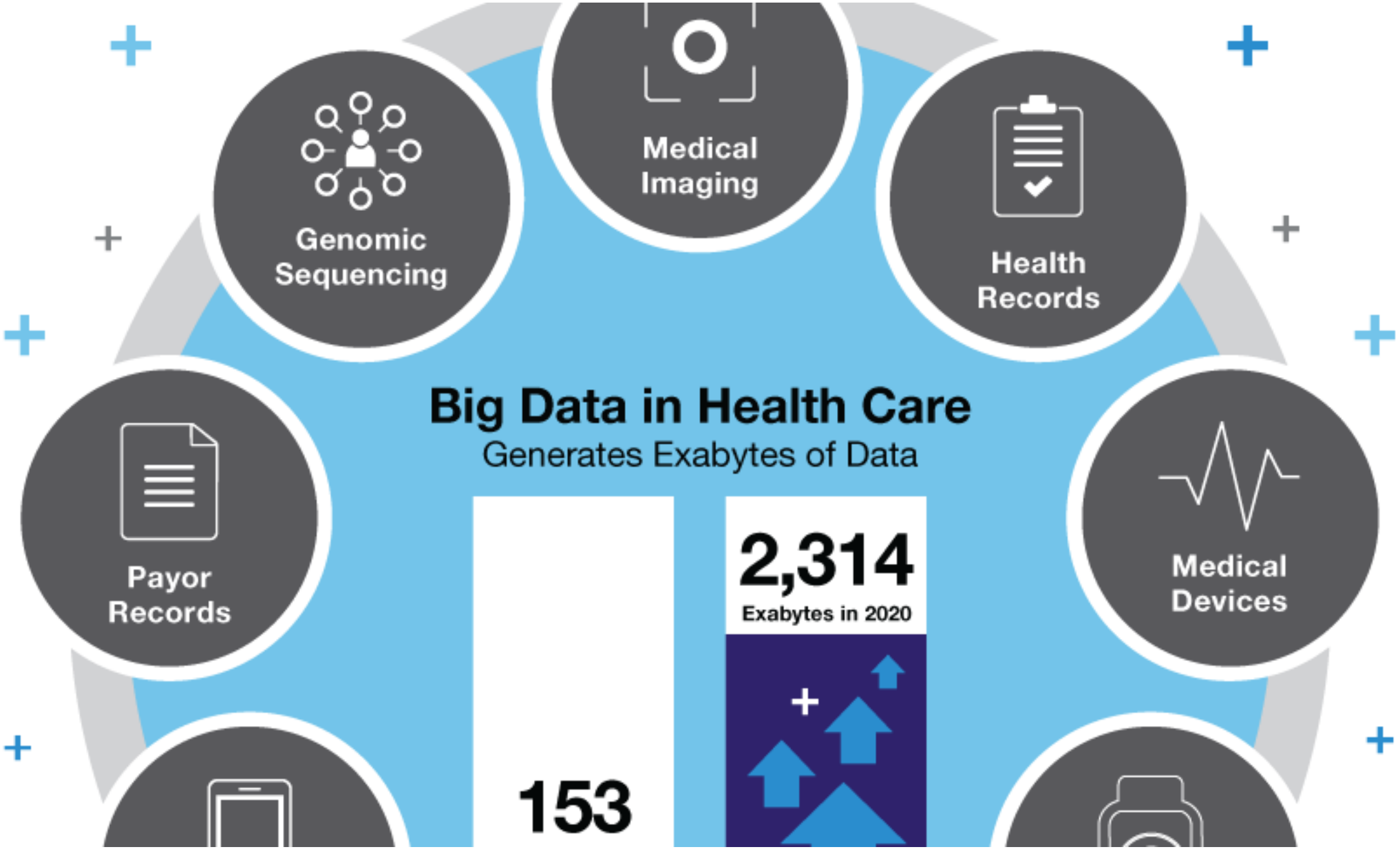


- This is the mechanism for the delivery of a diagnosis
- A diagnosis can inform the selection of management options for a patient with a suspected genetic disorder

- The initial differential diagnosis is used to determine the appropriate test strategy
- A test makes use of technologies in order to provide an accurate diagnosis
- A test can generate (secondary) genetic service requests

- This term captures the means and the methods by which a test is delivered
- The sequencing technologies could be, for example, sanger, next-generation, or whole genome

Payne K. PerMed 2017 May;14(3):235-247


Medical Imaging
Genomic Sequencing
Health Records
Payor Records
Medical Devices
Big Data in Health Care
Generates Exabytes of Data
2,314
Exabytes in 2020
153

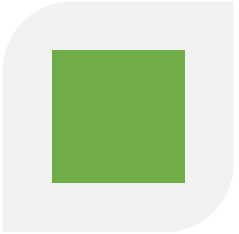
Modeling & Uncertainty

MARKOV-TYPE MODEL STRUCTURES INSUFFICIENT FOR CAPTURING LONG-TERM COSTS AND BENEFITS.

COMBINED AND COMPLEX TREATMENT PATHWAYS, COULD INCREASE LEVELS OF UNCERTAINTY ASSOCIATED WITH COST-EFECTIVENESS ESTIMATES

ANOTHER SOURCE OF UNCERTAINTY WILL BE THE UNIT COSTS, FOR EXAMPLE OF ‘OMICS’-BASED TESTS, WHICH VARY BY LABORATORY. SUCH TESTS MAY ALSO YIELD CONTINUOUS RESULTS, MEANING THAT THRESHOLDS MUST BE SET TO DETERMINE THE OUTCOME OF TESTING.

DETERMINATION OF THRESHOLDS SHOULD GO BEYOND ANALYSIS OF RECEIVER OPERATING CHARACTERISTIC CURVES



AN ADDITIONAL CONSIDERATION IS UNCERTAINTY AROUND THE BEHAVIOR OF CLINICIANS AND PATIENTS

Love-koh, J. PharmacoEconomics (2018) 36:1439–1451

How to reduce uncertainty

- Value of information analysis, was identified as key technique that could be beneficial to to quantify the extent of this uncertainty and the value of reducing it, through techniques such as expert elicitation.

- Along with more typical factors such as patient population size, the key determinants of value of information in PM will include the sensitivity and specificity of tests and predictions, and the intervention context.

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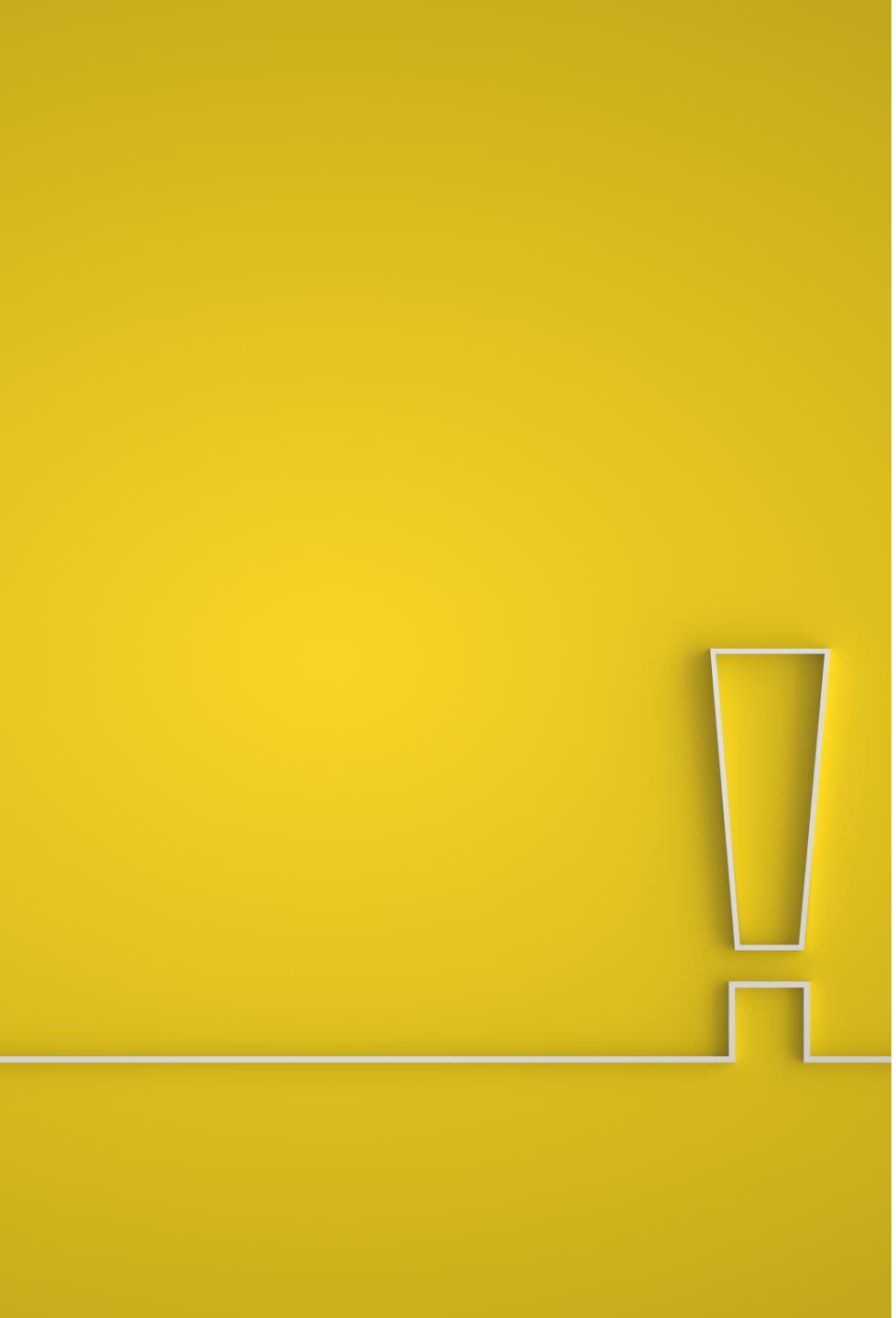
3	Target population	The target population for the intended use of the intervention should be stated.	PM sometimes fractures traditional clinical definitions. Consequence of testing in non-target populations also important.	Develop population definitions that define what is stratified and unstratified.
4	Comparators	Interventions and a reference case (the most common or frequently used care) must be chosen.	Test sequences combined with treatment lead to multiple strategies.	Require testing of all relevant strategies.
5	Perspective	In the Reference case, use the perspective of the publicly funded health system.	Similar to other non-PM interventions.	
6	Effectiveness	Use a systematic review to estimate the magnitude of effectiveness and adjust for "real-world" factors.	Compliance and adherence to testing important.	Further emphasis on adjustment for real world factors.
7	Time horizon	Use a time horizon based on the natural course of the condition.	Similar to other non-PM interventions.	
8	Modeling	Explain how and why model assumptions occur and whether the model has been validated.	Similar to other non-PM interventions.	
9	Valuing outcomes	Use appropriate preference-based measures to value differences between the intervention and alternatives in terms of HRQL. A representative sample of the public is the preferred source for preferences. Patients who have direct experience of the relevant health states may be an acceptable source.	Preference heterogeneity may exist. Valuing avoidance of unintended, harmful consequences poorly defined.	Further research on accounting for population preference heterogeneity and standards for disutility from harm.
10	Resource use and costs	Systematically identify, measure, and value resources that are relevant to the study perspective(s). Classify resources in categories that are appropriate to the relevant decision maker (e.g., primary care, drug plan, hospitals).	Costs of tests may depend on number of tests performed and be difficult to value. Analysts may also mistakenly omit costs of tests offered "free" (i.e., costs borne by manufacturer).	Improved guidance on accurate valuation of categories of costs from testing, including, opportunity, fixed, variable and other costs.
11	Discounting	In the Reference Case, discount the costs and health outcomes that occur beyond one year to present values at the (real) rate of 5% per year.	Similar to other non-PM interventions.	
12	Variability and uncertainty	Explore the effects of uncertainty (differences in effects reducible by further information) and variability (differences not reducible by further information)	Similar to other non-PM interventions.	

Husereau, D. Intl. J. of technology assessment in health care 30:2, 2014



Some remarks.

- PM will expand in the next decade: complex algorithms, health apps and ‘omics’-based tests.
- These technologies pose substantial benefit to patients, particularly to develop targeted therapies with greater efficiency.
- Early consideration of the evidence required by decision makers can improve evidence collection and analysis for PM technologies and services in very early stages of development and supporting the pace of HTA processes.

Recommendation	Possible approach	Timescale
To understand the current use of HTA to inform reimbursement and payer decisions for companion diagnostic medicines across Europe	Structured document review supported by a survey of key stakeholders	Short term
To identify and create a database of existing reimbursement and payer systems for diagnostics and medicines across Europe	Structured document review supported by a survey of key stakeholders	Short term
To identify how companion diagnostics are priced and/or charged for at the provider level across Europe	Survey of providers in hospitals and service commissioners	Short term
To understand the extent of variation in technologies and processes for the conduct of companion diagnostic testing within and across Europe	Survey of research and clinical laboratories	Short term
To understand how existing reimbursement and payer systems for diagnostics and medicines across Europe must be realigned to facilitate market entry	Semi-structured interviews and survey of key stakeholders	Medium term
To identify incentives to encourage manufacturers to invest in the production of a robust evidence base supporting the clinical effectiveness and cost-effectiveness of companion diagnostic medicines	Establish a mixed working group of key HTA bodies and manufacturers	Medium to long term
To describe and quantify gaps in the evidence base and the added value of future research to reduce current uncertainties to support the introduction of companion diagnostics	Economic modeling with formal value of information methods	Medium term
To identify and target national funding for research to understand the added value of technologies	Establish a working group of HTA bodies and research funding bodies	Medium to long term
To align the use of HTA for the reimbursement of companion diagnostics in line with existing practice for medicines	Establish a working group of key HTA bodies	Long term
To produce clear and explicit guidance on the evidence that decision makers working at national and local provider levels would like to support the reimbursement of companion medicine diagnostics	Establish a mixed working group of key stakeholders including HTA bodies, manufacturers, and hospital providers	Long term

Payne, K. VALUE IN HEALTH 16 (2013)S32 – S38

Toward HTA of WGS-based diagnostic tests: some practical suggestions

- Long-term, on-going issues are focusing on methodological and organizational challenges; empirical research is required to address some of the challenges outlined.
- In the short term, there are a number of practical steps which will begin to address these challenges.
- The transparent setting of Europe-wide agreed tariff structures would facilitate the design and conduct of HTAs of WGS-based diagnostic tests.
- The PICO framework could be used by multidisciplinary teams, including patient representatives, to facilitate comprehensive description of interventions and comparators for HTA.
- Continuation of trans-European working toward the collation of epidemiological data will inform HTA practitioners to define relevant patient populations and provide data for economic modeling.
- The lack of availability of a treatment option could be a simple criterion to use to set aside an HTA process for WGS-based diagnostic tests for inherited rare conditions but further research is required to inform how to conduct such HTAs and take into account the potential opportunity cost (health gain lost) by using HTA that does not focus on quantifying health gain to populations.
- A repository of openly available economic models would be a valuable resource for HTA practitioners working toward HTAs of WGS-based diagnostic tests.

Conclusion & future perspective

- Implementation of practical suggestions requires joined-up, multidisciplinary working across European healthcare systems.
- Trans-European networks and consortia which foster links between academics, clinicians and scientists are well-placed to identify and address emergent HTA-related challenges as the need to integrate genomic-based diagnostics into mainstream medicine becomes more apparent.

- However there is no clear path about the role of HTA and PM in EU and LATAM.
- Role of expert consultation and multi-stakeholder involvement is relevant to overcome challenges possessed by these technologies.

Payne K. PerMed 2017 May;14(3):235-247

Thank you

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