A pilot study to assess feasibility of value based pricing in Cyprus through pharmacoeconomic modeling and assessment of its operational framework: sorafenib for second line renal cell cancer

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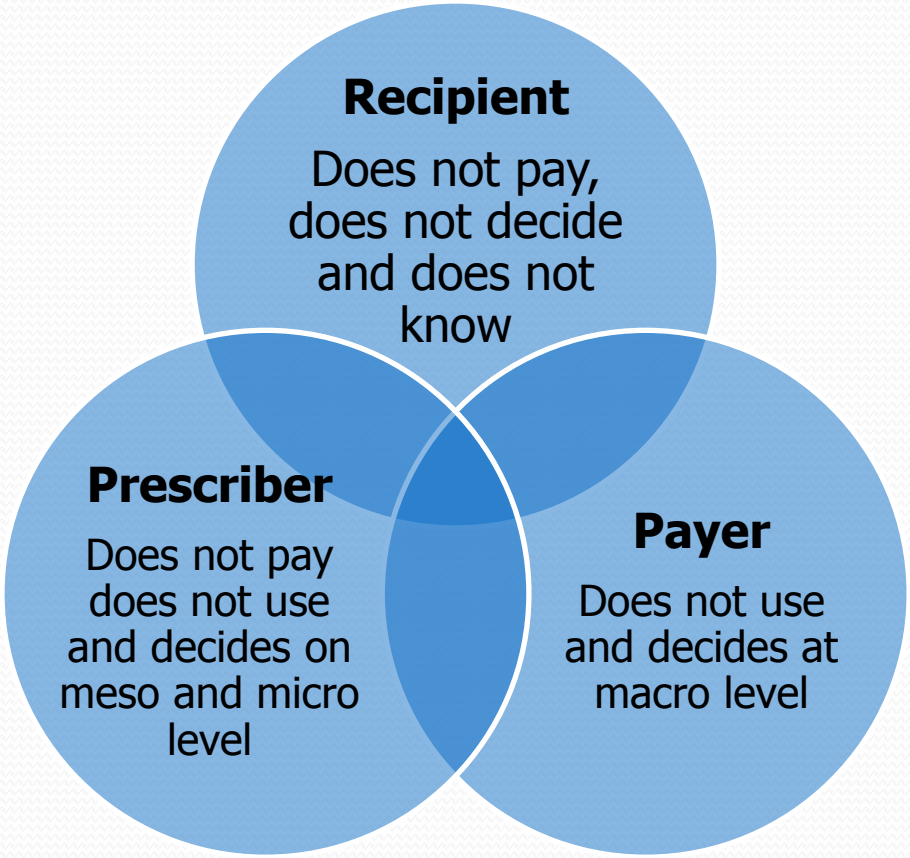
Malta as the pinnacle of uncertainty

Structure of pharmaceutical market



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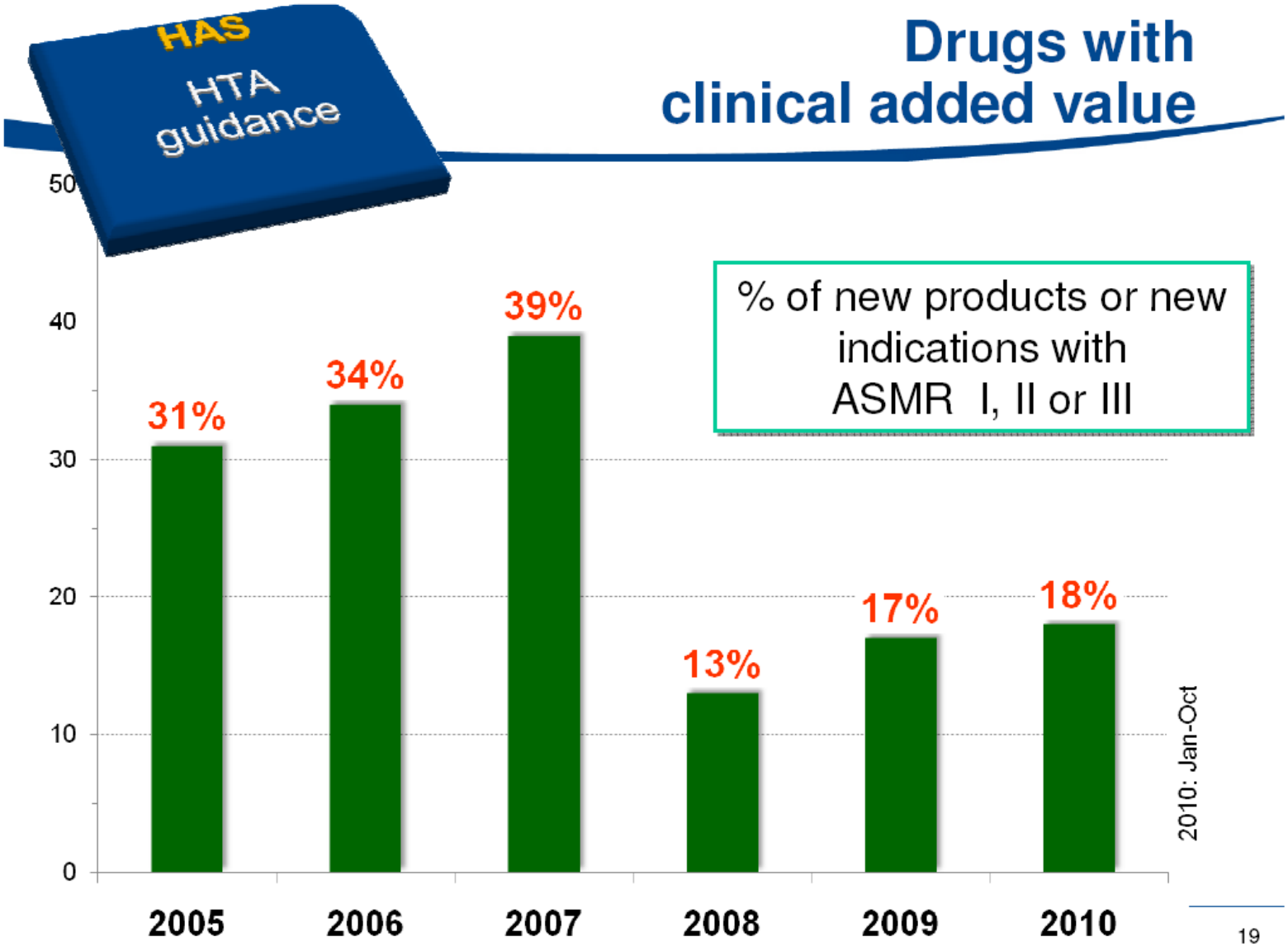
Do we get enough innovation?



Increase of prices of new products, compared to existing ones, for the same indication

Acute Care

- Major health Benefit 2.97
- Modest health Benefit 1.72
- Marginal health Benefit (or equivalence) 1.23

Luz and Comanor(1998)

Chronic Diseases

- Major health Benefit 2.07
- Mild health Benefit 1.19
- Marginal health Benefit (or equivalence) 0.94

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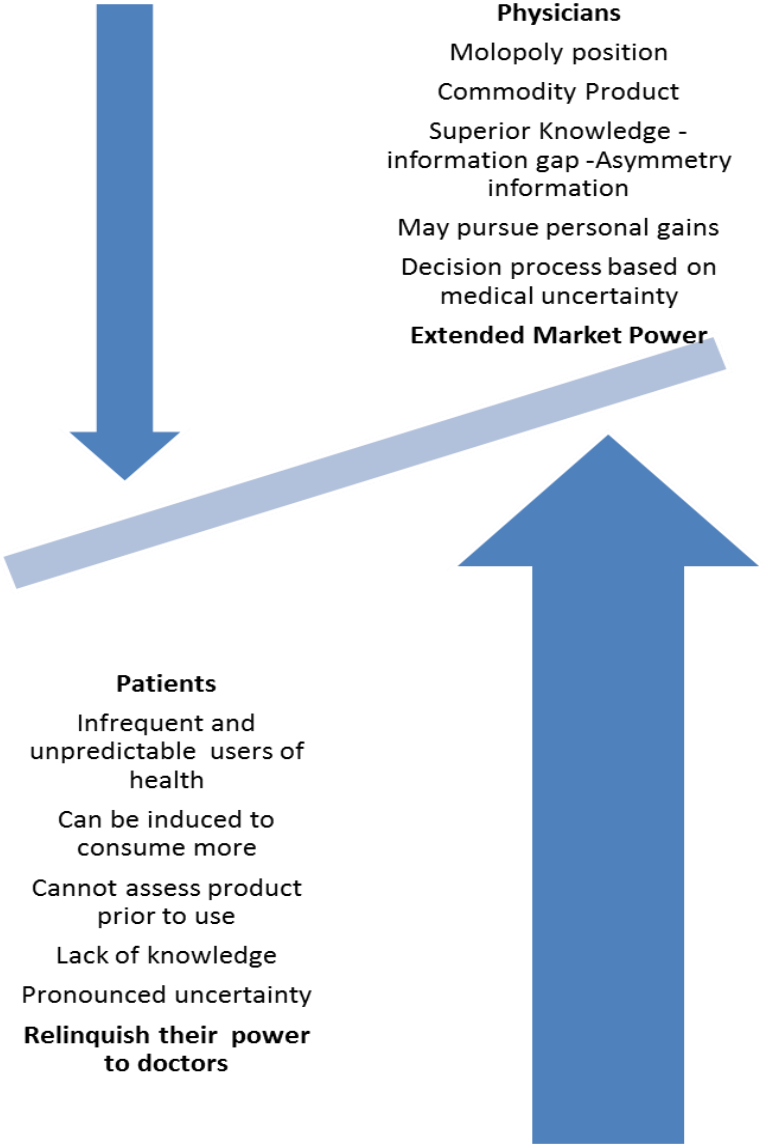

Petrou P Demand side measures to address supplier side demand? A quasi experimental study for inappropriate laboratory utilization from a payer perspective in Cyprus. Working Paper

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Uncertainty in the Pharmaceutical Market

- Biological Uncertainty
  - Prevalence, severity and outbreaks of diseases.
- Price Uncertainty
  - Does the price reflects the real value of the product (social, medical, economical)?
- Utilization Uncertainty
  - Does the prescribing pattern maximises the utility of each product? Are physicians influenced by other attributes of the product? Vested interests and subconscious rapport
  - "In the 1980's physicians were trying to sing the right song. Nowadays, they are trying to sing the song right." British Pharmacopeia.

Naming and Branding

- Art and Science
  - Subconscious rapport of industry to the physician, interacting at the emotional level,
  - Confirms Credibility
  - Build loyalty
  - Create relationship with doctor –adds value

- Use of linguistic tricks
  - plosive letters (P, T or D) to convey power,
  - fricative letters (X, F, S or Z) to imply speed

- Obsession with X e.g. Nexium, Celebrex, Xanax, Zyban and Zithromax.
  - look better in print,
  - make sounds people like saying
  - are associated with innovation

- The same applies for studies - Forward looking, positive, encouraging, innovative, everlasting subconscious messages to capture prescriber: Attract, Attack, Prove ATHENA, APOLLO, HERMES, ZEUS and JUPITER.

- Think of an animal or adjective with positive connotations, and chances are, there's a study attached to it.

Demand and supply-side measures

- **Supply- Side Measures**
  - directly or indirectly affecting *prices*, which affects dispensed volumes
  - free *pricing*
  - direct price controls
  - cost-plus and *cost pricing*
  - *average pricing* and international *price*
  - comparisons
  - profit control
  - reference *pricing*
  - positive and negative lists and other *price* control measures
- **Demand-Side measures**
  - implementing good prescribing practices
  - budgets for physicians
  - generic policies
  - practice guidelines
  - monitoring the authorizing behavior of physicians
  - disease management schemes
  - co-payments
  - the impact of allowing products over-the-counter
  - health promotion programs

Pharmaceutical Pricing

- The most important, potent, prominent and debatable supply side measure of pharmaceuticals.
- Differs significantly from pricing in other markets, due to the flaws of pharmaceutical market.
- A major source of uncertainty:

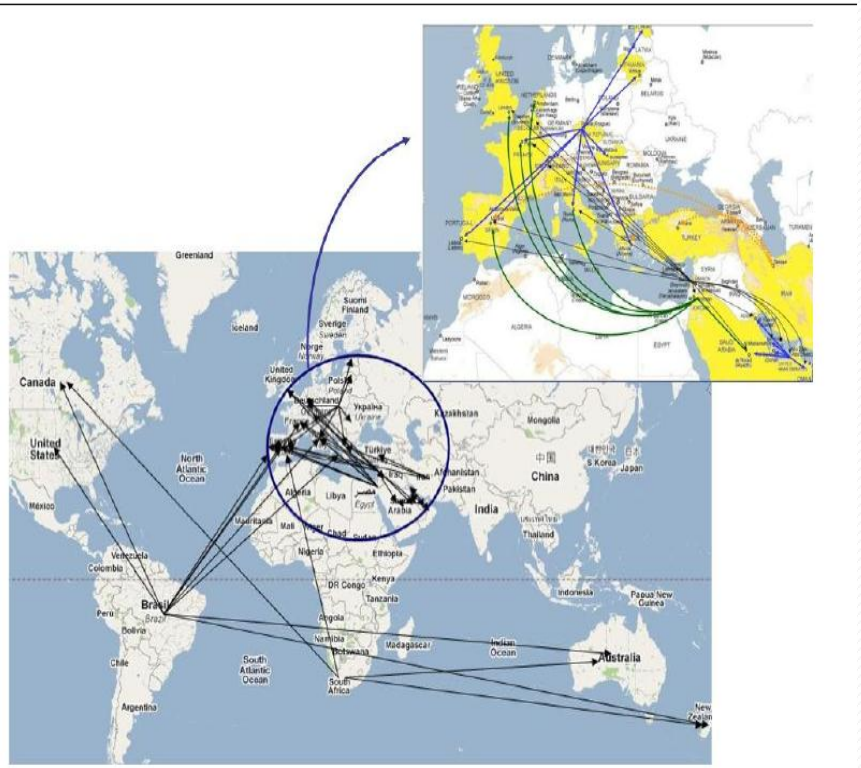
  "How much utility we get back"

External Price Reference as a source of uncertainty

- Simplicity of reference pricing makes it an ideal approach especially for smaller countries.
- It's path dependant, thus leading to heavily predictable outcomes.
- These advantages come at the cost of lack of any theoretical basis.
- Country selection is performed on secondary factors, such as geographical proximity and access to prices.
- Countries revise prices with significant time variation. Therefore prices in one country may not be relevant in a referencing one.
- Following countries blindfold trail behind reference ones and the risks of dissemination of flawed pricing approaches (too high or too low prices) is eminent.
- WHO/HAI Project Medicine Prices and Availability states that it's doubtful whether the External Referencing Prices are "*appropriate, efficient or optimal in accordance with any objective criterion*".

WHO: Working Paper 1: External Reference Pricing. WHO/HAI Project on Medicine Prices and Availability. 2011. (Online). Available at http://www.haiweb.org/medicineprices/05062011/ERP%20final%20May2011.pdf> [Last assessed on September 25 2012]

Significant interrelation and interdependence between many countries



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Significant interrelation and interdependence between many countries (continues)

- Introduction of clawback/ payback schemes as a mechanism to avoid budget overshooting: high prices and avoidance of price reductions which can escalate to a rolling spillover effect on the other reference countries.
- Clawback/ payback schemes alleviate the impact of high prices locally, but these schemes are not taken into consideration by the ncountries that reference.
- Selection of right price is trivial since products may carry many prices (retail, gross retail, reimbursement, ex-factory, official wholesale).
- The referencing system reaches a steady state following the convergence of prices and further reductions are not anticipated.
- Reference pricing does not reward innovation.

Value Based Pricing

- A simple answer to a simple question (though requiring a complex intermediate procedure).
- A paradigm shift from volume to value, aiming to convert the health benefits that the product delivers, which exceed the health benefits displaced in the broader health system and society due to additional cost incurred, into monetary value.
- Incorporation of the product's value into its price in the concept of a holistic pathway.
- It safeguards access to effective and innovative drugs by setting a price that reflects the utility created.
- From an industry perspective, this constitutes a clear motive to pursue innovation.
- From a payer's perspective this leads to optimality of available resources.

Camps-Walsh G, Aivas I, Barratt H: How can value-based pricing improve access to and adoption of new treatments? 2020health 2009, 1–105.
Brown MM, Brown GC, Sharma S: Evidence-Based to Value-Based Medicine.Chicago: AMA Press; 2005:151–265.

Our study

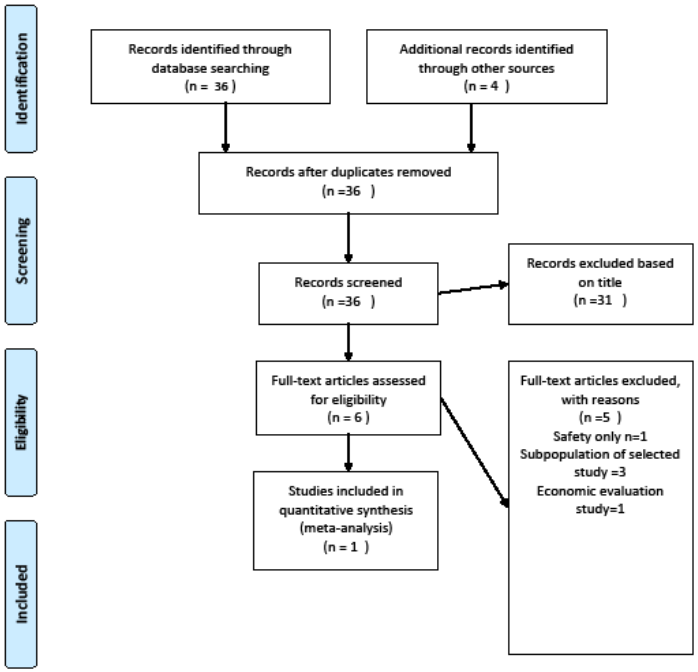
- In the USA, oncology medicines expenditure rose four fold in seven years.
- In Cyprus, a two fold increase of expenditure from 2005 to 2011 occurred.
- The dominant prescribing pattern in the oncology category is the shift from cheaper to more expensive new products.
- Sorafenib for m Renal cell cancer:
  - Orphan Drug
  - Monopoly status
  - High price
  - Unmet medical need
  - Scarce data= Increased uncertainty

Bach PB: Limits on medicare's ability to control rising spending on cancer drugs. New Engl J Med 2009, 360:626–633.
Petrou P: Power of r- Pharmaceutical sales decomposition in Cyprus public health care sector. Any lessons learned? Expert reviews of pharmacoeconomics and outcomes research. Expert Rev Pharmacoecon Outcomes Res 2014, 14(2):289–300.

Getting the Data

Table 2.

Flow Diagram of literature review of Sorafenib in Second line renal cell carcinoma



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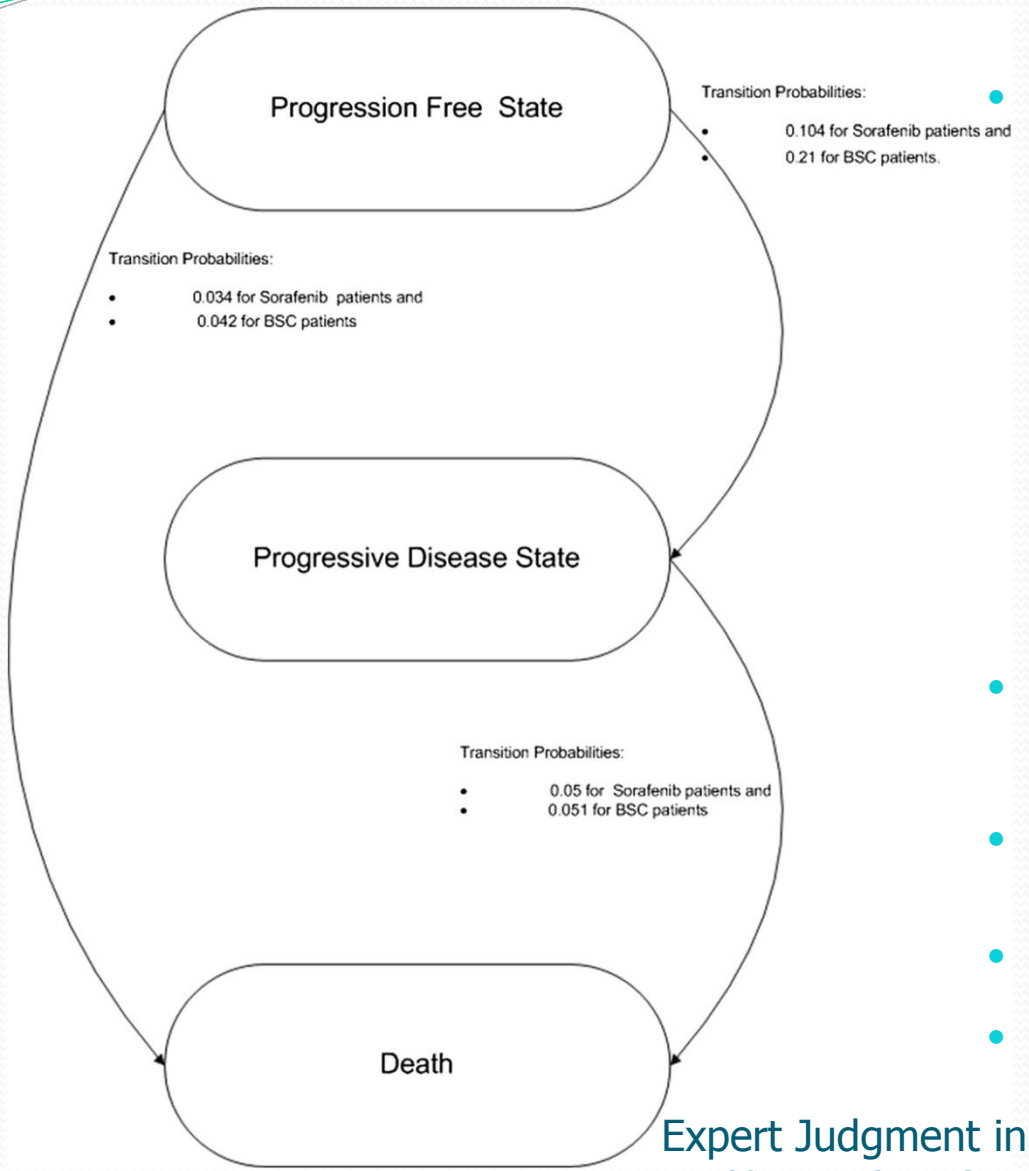
Markov Model



- A memoryless process which describes the evolution of disease between health states in a stochastic way based on the transition probabilities, which depend only on the current state of the process and not on previous states. Three non- absorbing health states were identified:
  - Progression-free survival(PFS),
  - Progression disease (PD)
  - Death

  Risk of an event
  =[1-(0.5) *(1/median time to event)*
  $P=1-e^{-R}$
  $R=-ln(0.5)/$*time to event/ number of treatment cycles)*

- Model was loaded with an initial cohort of 1,000 patients on the second line of treatment with sorafenib with an indication of metastasis.
- The first 50,000 iterations of simulation to were discharged to ensure stability of the model
- Another 50,000 iterations were performed to ensure convergence and accuracy of data.
- We checked convergence through trace plots of samples and standard error of the results

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Distributions

- Probability of progression and probability of death follow a beta distribution since they are bounded between 0 and 1.
- Sorafenib costs were denoted by a uniform distribution as per the recommended (approved) daily dosage since we assume that all patients receive recommended daily dose.
- We adopted the health state utilities as reported by Thomson which were assessed through the use of UK EQ-5D: health state utilities of 0.76 (s.e. 0.03) for PFS and 0.68 (s.e. 0.04) for PD. Since utility value are defined between 0 and 1, we assume that they follow a beta distribution as following:
  - Progression Free State (153.26, 48.4),
  - Progressive disease state (91.8,43.2).

Thompson Coon J, Hoyle M, Green C, Liu Z, Welch K, Moxham T, Stein K: Bevacizumab, sorafenib tosylate, sunitinib and temsirolimus for renal cell carcinoma:a systematic review and economic evaluation. Health Technol Assess 2010, 14(2):1–184.

Briggs A: Probabilistic Cost-Effectiveness Modelling: Overview of Methods and Challenges with an interactive Illustration. 7th Annual Meeting ISPOR MAY 2002: Rotterdam ,The Netherlands. 2002.

Ara R, Wailoo AJ: NICE DSU Technical Support document 12:The use of health state utility values in decision models. 2011, Available at http://www.nicedsu.org.uk last assessed November 2013/.

Distributions (continues)

- Cost distribution of general medical and other pharmaceutical costs (excluding sorafenib cost) was assumed to follow a gamma distribution, and method of moments was applied in order to estimate parameters of this distribution.

- The assumption is that if there is a random sample from a gamma distribution X1, X2, X3, ……Xn, and a and b are the unknown parameters of gamma distribution, then the expected value equals E[X] = ab and E[X2] = ab2 + a2b2 Therefore, we have to find the moments estimators by solving the two following equations:

$$\frac{1}{n}\sum_{i=1}^{n} X_i = \overline{X} = \alpha\beta \qquad \frac{1}{n}\sum_{i=1}^{n} X_i^2 = \alpha\beta^2 + \alpha^2\beta^2$$

The solution results to:

$$\alpha = (\overline{X} / \beta) \text{ and } \beta = [\{(1/n)\sum_{i=1}^{n} X_i^2 - \overline{X}^2\} / \overline{X}]$$

Dias S, Welton NJ, Sutton AJ, Ades AE: Evidence synthesis for decision making the baseline natural history model. Med Decis Making 2013, 33(5):657–670.
Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009) Preferred Reporting Items for Systematic Reviews and Meta-Analyses: the PRISMA statement. PLoS Med 2009, 6(6):e1000097. doi:10.1371/journal. pmed1000097.

Distributions (continue)

BSC ARM	Medical and other pharmaceutical cost in Progression free stage	Progression stage	SORAFENIB ARM	Sorafenib cost	Medical and other pharmaceutical cost in Progression free stage	Cost in the progression stage 1st and 2nd month	3nd Month and further on
Cost (euro) 2012	218	770		2880	357	1499	770
Type of Distribution	Gamma	Gamma		Uniform	Gamma	Gamma	Gamma
Distribution parameters α,β	(1336, 4.8)	(3696, 4.8)		(2880,2900)	(1714, 4.8)	(7196, 4.8)	(3696, 4.8)

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Results

	Willingness to pay Threshold	20,000	40,000	60,000	>100,00
Cost of sorafenib arm		10620.0 (CI 95% 9022.0-12490.0)	13760 (CI 95% 11680.0-16290.0)	16996 (CI 95%14370.0-20120.0)	23806.0 (CI 95% 20,000 - 28220)
Cost of bsc arm		7336.0 (CI 95%: 6327.0-8468.0)	7336.0 (CI 95% : 6327.0-8468.0)	7336.0 (CI 95% : 6327.0-8468.0)	7336.0 (CI 95% : 6327.0-8468.0)
Incremental QALY gains		0,1605 QALY	0,1605 QALY	0,1605 QALY	0,1605 QALY
Incremental Cost		3284	6424	9630	16470
VBP of sorafenib		**810**	**1325**	**1816**	**2880**

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Sensitivity Analysis

Parameter	Baseline Value	Sensitivity Analysis	New Price	ICER	BASE CASE
Sorafenib price	1851 (per month)	50% reduction	925	24,190	60,00
TIME HORIZON	10 YEARS	5 YEARS	1860	60,266	60,000
Discounting	3.5	0	2455	45,279	60,000
Discounting	3.5	1.5	2124	51,025	60,000
Discounting	3.5	5	1695	67,203	60,000
QALY	0.76 – 0.68	0,836 0.748	2013	54,738	60,000
QALY	0.76 – 0.68	0.684- 0.612	1711	66,863	60,000
Medical and other pharmaceutical costs		Increase 20%	1926	57,407	60,000
Medical and other pharmaceutical costs		Decrease 20%	1802	62,282	60,000
Decrease of PFS 10%			1655	68,853	60,000
Decrease of PFS and OS 10%			1580	72,374	60,000
Increase of PFS and OS 10%			2030	53,300	60,000
Increase of OS 10%			1905	58,329	60,000
Increase of PFS 10%			1987	55,701	60,000
Decrease of OS 10%			1790	62,695	60,000

Are we there yet ?

- Are we are satisfied with one threshold level ? Or shall we introduce varying thresholds level (severity specific and weighted?).
- What about 2nd Indication?
- A higher WTP threshold for conditions with greater burden of illness, such as rare and orphan diseases, end of life treatment, highly innovative products and medicines that exhibit wider societal benefits, such as benefits to careers.
- Potential extra weight of QALY in end of life treatments while others debate that even a QALY at the end of life actually varies according to the way it was obtained, with gain in palliative care being superior to gains in life expectancy.
- Since all health programs actually compete for funds it's possible that this diversity may be beneficial for some patients and injurious for others.
- Ginette Camps-Walsh suggests 5 different categories of threshold within NHS which differentiate acute, chronic, paediatric, rare and end of life diseases. The categories above have varying degrees of treatment options and as a result, each category has diverse unmet medical needs.

Towse A: Should NICE's threshold range for cost per QALY be raised? Yes. BMJ 2009, 338:181.
National Institute for Clinical Excellence (2009a): Update report on the Application of the 'End-of- Life' Supplementary Advice in Health Technology Appraisals. London; 2009.
Pinto-Prades J-L, Fernando-Ignacio S-M, Corbacho B: Valuing qalys at the end of Life. Seville, Spain: Andalusian Agency for Health Technology Assessment; 2012.
Mason H, Jones-Lee M, Donaldson C: Modelling the monetary value of a QALY: A new approach based on UK data. Health Econ 2009,18(8):933–950

Challenges

- Available health state measurement tools can deliver varying results and it's also documented that patients in different stages of the same disease have different perception of time and health state preferences.

- These findings create further complications regarding the selection of endpoints of the study (Overall survival or Progression free survival) which must be consistent in order to ensure homogeneity among potentially comparative products.

- Comparator selection and specifically the base care product, is of paramount importance. In a time series setting, the price of future products will be a step-up dependant based on past and current value based prices.

- We compared sorafenib to BSC, with BSC being the base case product. Upon future introduction of axitinib, its price will greatly depend on price of sorafenib and there will be notable differences between sorafenib's reference (2880 euro) and sorafenib' s value based price (1816 euro).

Hemmett L, Holmes J, Barnes M, Russell N: What drives quality of life in multiple sclerosis? QJM: An Int J Med 2004, 97(10):671–676.

Maor Y, King M, Olmer L, Mozes B: A comparison of three measures: the time trade-off technique, global health-related quality of life and the SF-36 in dialysis patients. J Clin Epidemiol 2001, 54:565–570.

Hanneke WM, Van L, Schilderman J, Constans AHHVM, Verhagen M, Prins J:Time perception of cancer patients without evidence of disease and advanced cancer patients in a palliative, end-of-life-care setting. Cancer Nurs 2011, 34(6):453

Is this the end of the pricing as we know it?

- The level of complexity further rises given that in oncology regimens, it's not rare to encounter expensive adjuvant products. It's still unknown how to address this issue regarding products that were priced ex post and products that will be priced ex ante.
- Another decisive task is to express all values into money: Net-benefit; multicriteria decision analysis, by using weight value for each benefit type.
- Value based pricing is expected to engage R & D companies in a quest for really innovative products.
- Nevertheless, it may also deter companies from investing into territories, in which marginal benefits are anticipated.
- Another pending issue is the pricing of equivalent products and the concern that this will impede further price competitions which have led to massive reductions in some therapeutic categories, such as statins.

Devlin N, Sussex J: Incorporating Multiple Criteria in HTA: Methods and Processes. London: Office of Health Economics; 2011
Kanavos P, Taylor D, Manning J, Carr M: Implementing Value Based Pricing for Medicines An introduction. London: University of London; 2010
Hughes D: Value-based pricing incentive for innovation or zero net benefit? Pharmacoeconomics 2011, 29(9):731–735. 1170-7690/11/0009-0731/$49.95/0.

Homework

- The determination of affordability thresholds and overall affordability.
- The relative lack of identifying, measuring and valuing additional health benefits.
- Conversion from value to price.
- Data aggregation in heterogeneity population.
- Inherent challenges of measuring and comparing utilities of different types, different diseases and different stages of the same disease.
- Time lapse between availability of clinical data and best practice development.
- Ambiguity regarding optimal approaches of late external benefits that cannot be captured in the short term analysis

Kanavos PK, Nicod E, Espin J, Van Den Aardweg S: Short- and Long-Term Effects of Value-Based Pricing vs. External Price Referencing. Brussels: LSE Health – London School of Economics, Andalusian School of Public Health; 2010.

Homework (continues)

- As proved by our analysis value based pricing does not result in high pharmaceutical prices when society's WTP is known.
- VBP, under a specific context, it can be considered as a cost containment tool.
- This does not come under surprise since oncology products due to their innovative mode of action, high R & D costs and considerable failure rates ask for higher prices.
- In our study we transferred health utilities from published study. Value based pricing framework in other countries, such as Germany provides that a product gets a provisional price, and afterwards "real life effectiveness data" are gathered, which will be utilized to set a value based price . For new products this preferably has to be carried out in national level. This is in line with other approaches which provide that new products get a price based on an ex ante evaluation while existing products get a price based on a rolling ex post evaluation.

Persson U: Value Based Pricing in Sweden: Seminar Briefing no12. London: Office of Health Economics; 2012:1–10.

Kielstra P: Reinventing Biopharma: Strategies for an Evolving Marketplace. The Value Challenge. London: Economist intelligence Unit; 2012

Greiner W: Germany's drug pricing after AMNOG – What comes next? In 7th American & German Healthcare Forum Minneapolis, June 21st. Minneapolis, USA; 2011.

Mcguire A, Raikou M, Kanavos P: Pricing pharmaceuticals: Value based pricing in what sense? Eurohealth 2008, 14(2):3–5.

Conclusions

- New approaches are needed to minimise uncertainty in decision making in the pharmaceutical sector.
- VBP is on the right course and can be a valuable partner.
- Many boxes must be ticked before this scheme goes mainstream.

Panagiotis Petrou, Michael A Talias. A pilot study to assess feasibility of value based pricing in Cyprus through pharmacoeconomic modelling and assessment of its operational framework: sorafenib for second line renal cell cancer *Cost Effectiveness and Resource Allocation* 2014, **12**:12