Pharmaco-economic aspects of pharmacogenomics and personalized medicine

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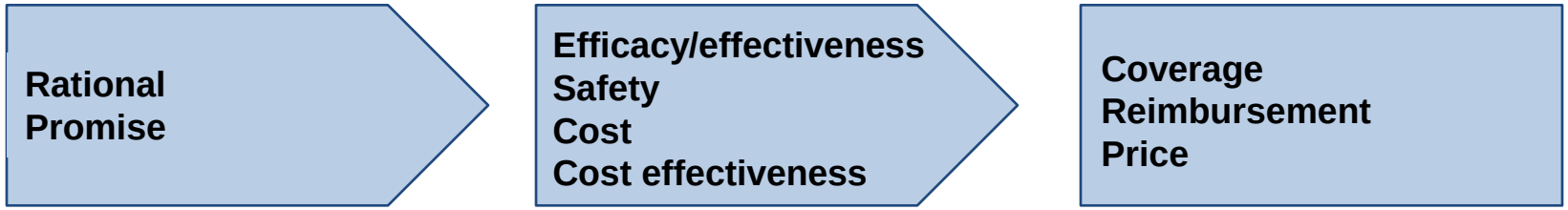
2nd ESPT Summer School on Pharmacogenomics and Theranostics
June 10 2014
Rome

Objectives

- Rational for personalized medicine, promise and perception
- Basic pharmaco-economic methodology and application to personalized medicine
- Payer approach towards personalized medicine and other expensive drugs
- Key challenges and requirements for personalized medicine

Flow


Rational
Promise
Efficacy/effectiveness
Safety
Cost
Cost effectiveness
Coverage
Reimbursement
Price

Today, personalized medicine is shaped by biomarker based stratified therapy, applied to distinct patient groups

Conventional therapy

- **No biomarker test**
- **No stratification or individualization**

"One size fits all"

Stratified therapy
Biomarker based therapy

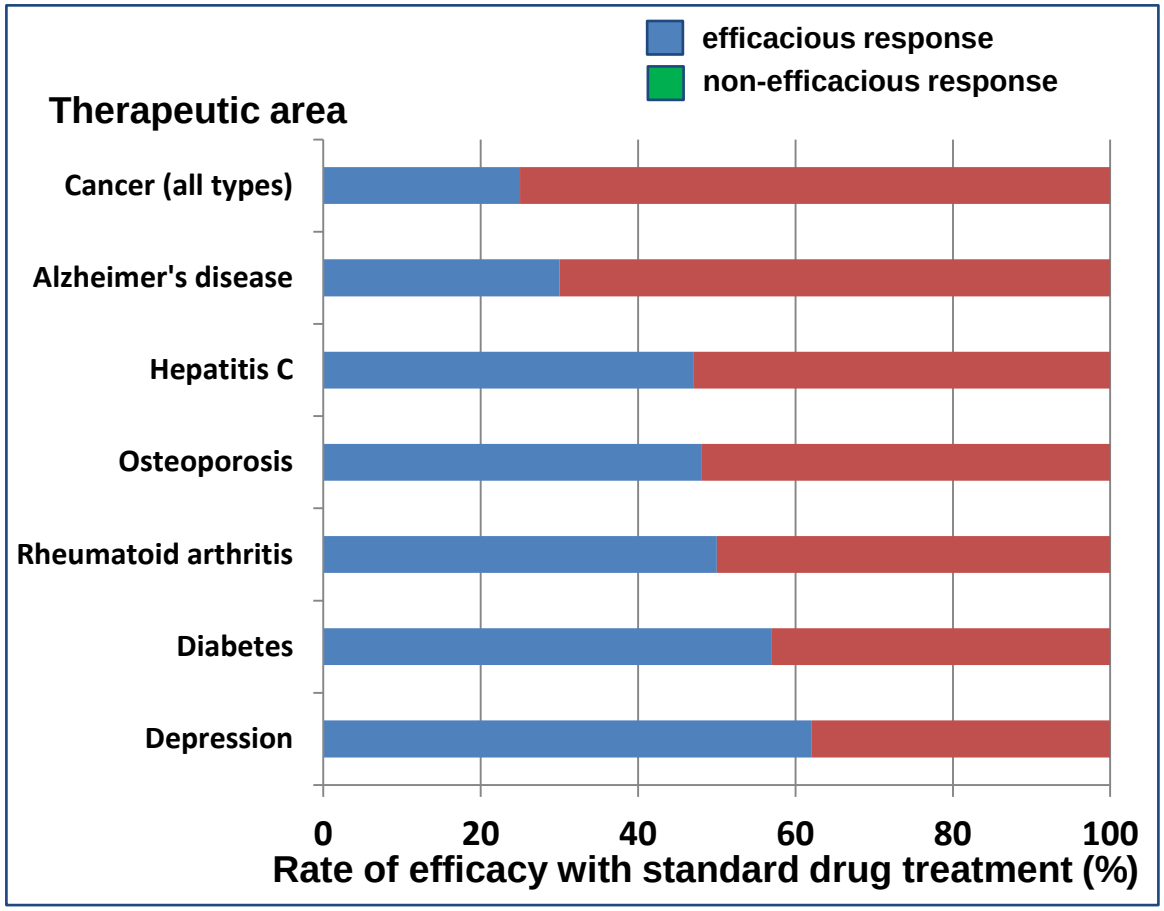
- **Prognostic biomarker (e.g. Oncotype® DX, Femtelle®)**
  course of disease
- **Predictive biomarker (e.g. G551D-CFTR, HER-2)**
  response to therapy
- **Pharmacodynamic/pharmacokinetic biomarker (e.g. PGS Statins)**
  dosing, patient-(group) individual therapy, gender

- **Biomarker**
- **Biomarker supported decision making and therapy**
- **Companion diagnostics**

"Personalized medicine seeks to improve stratification and timing of health care by utilizing biological information and biomarkers on the level of molecular disease pathways, genetics, proteonomics as well as metabolomics

Schleidgen et al. 2013

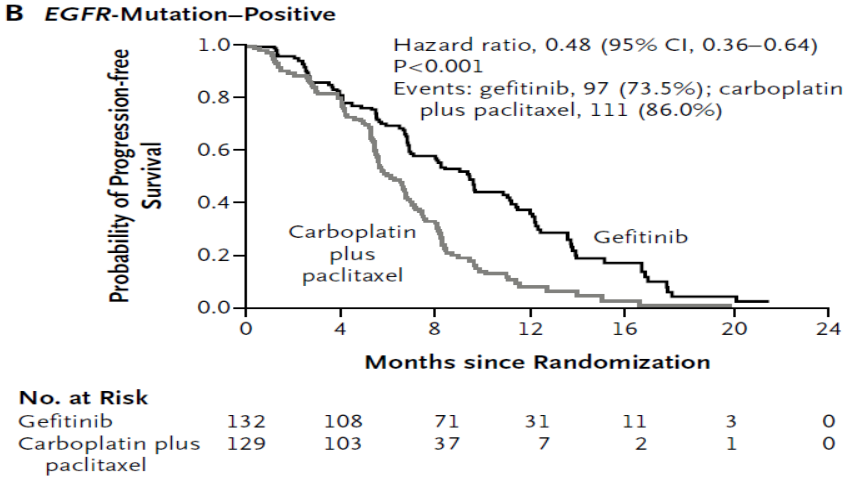
High unmet need and continuing demand for efficacious treatments serves as key driver for personalized medicine

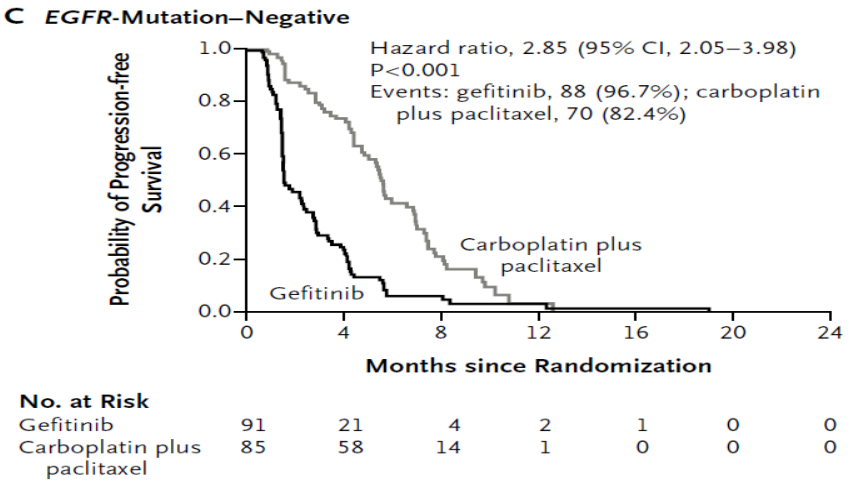


modified after Aspinall MG and Hamermesh RG (2007)

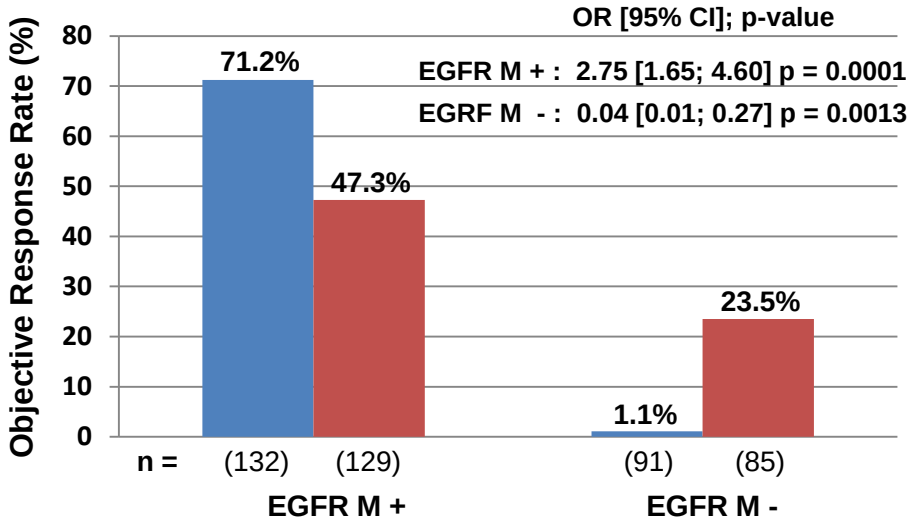
- Available standard drug treatments are deemed to provide sufficient therapeutic benefit for a fraction of patients only
- New targeted therapies may allow to treat more people with efficacious treatments
- Additional therapeutic advances expected from pharmacogenomics, biomarkers and targeted therapies

Case study: Gefitinib (IRESSA) improves outcomes in patients with advanced NSCL, who are EGFR positive





source: Mok et al. 2009; NEJM 361, 947-957



"Gefitinib, a tyrosine kinase inhibitor, is licensed for the treatment of locally advanced or metastatic non-small cell lung cancer with activating mutations of epidemal growth factor receptor"

source: BNF 66; Sept. 2013

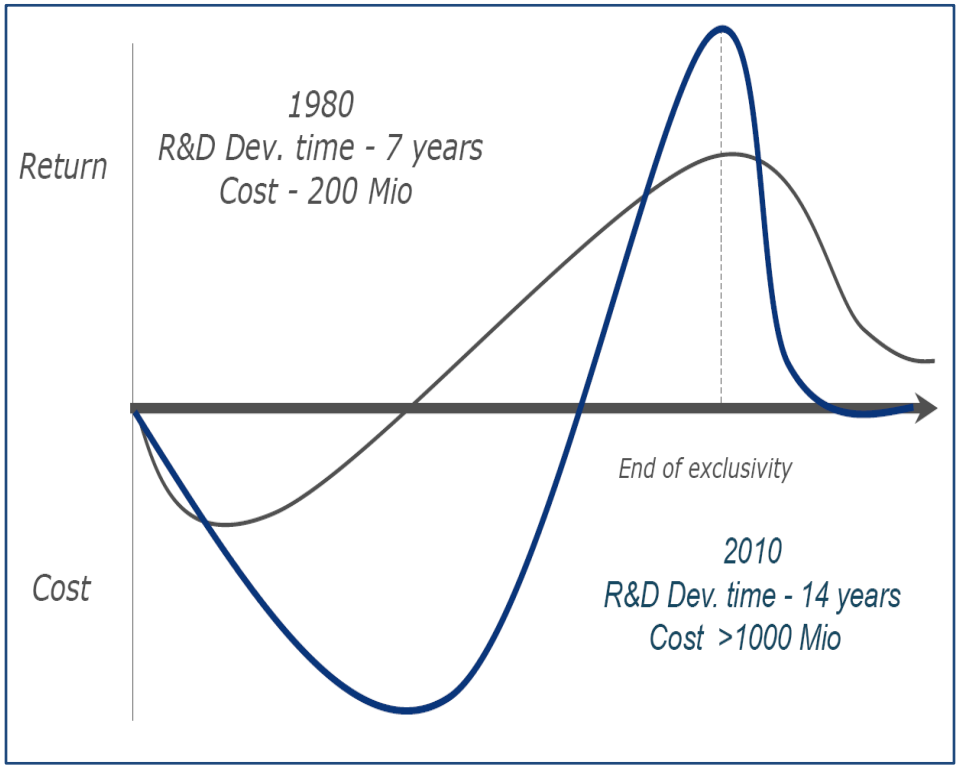
Perception of personalized medicine by physicians, patients, industry and payers: heterogeneous expectations and concerns dominate

The perception of personalized medicine varies between key stakeholders with all stakeholders considering the value for money and cost of new treatments a central decision criteria

Physicians/patients	Industry	Payers
• Physicians welcome the availability of additional treatment options that offer improved efficacy and safety • Patients hope for curative treatments that improve the health status • Payers and physicians are often disappointed about the incremental benefit and cost of personalized medicine	• Perceived as major growth area for the future • Commercial exploitation of new and promising treatment concept • Improve the success rate in development • Accelerate regulatory and payer approval and extend on-patent	• Perceived with high ambiguity because the implications are not yet clear • Hope for savings resulting from targeted administration of drugs • Concern that new cost that may exceed the saving potential • Potential to change the established value for money ratio in health care
• **Perceived with great aspiration but promise not yet fulfilled**	• **Personalized medicine is an attractive area that may allow to enter into a promising and rewarding new area of sciences and business**	• **Affordability is the key priority. Can payers afford all the good things coming along with the budget that is available?**

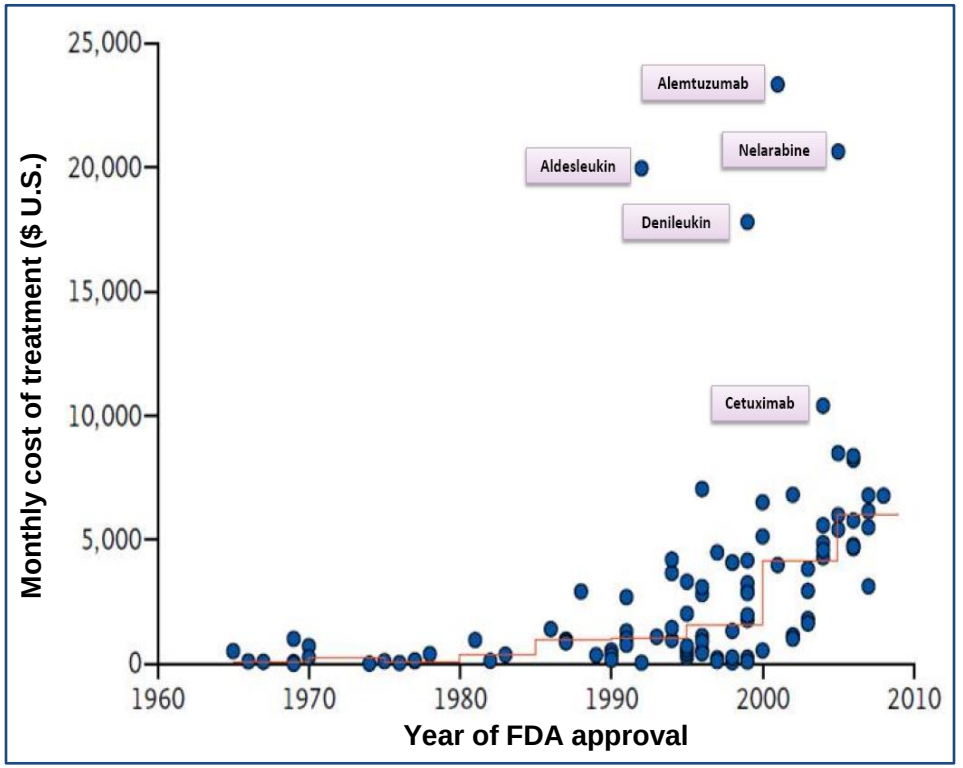
Rising development cost, extended development time and increasing cost of new treatments will shape the approach towards personalized medicine of industry and payers

Industry view



source: Lauwers L (2010)

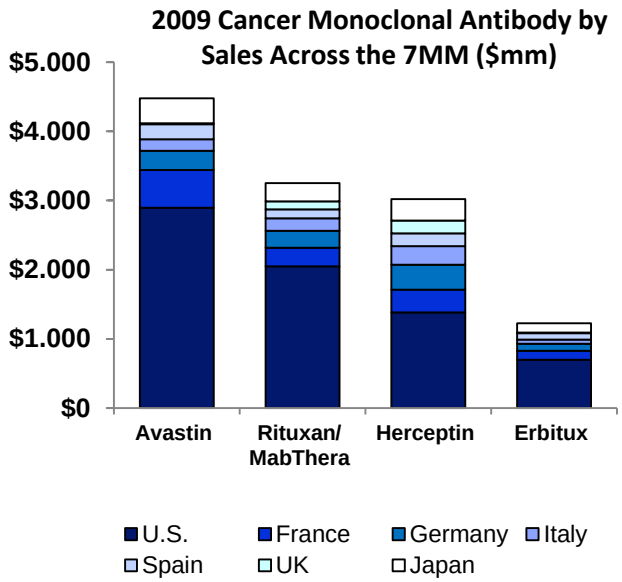
Payer view

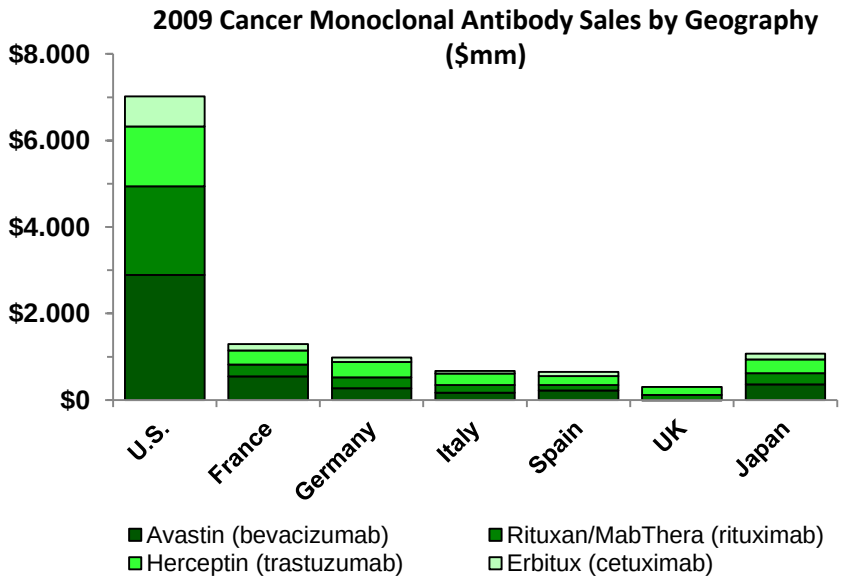


source: Bach (2009)

As spending for existing biologics is already high, payers are concerned about the rise in cost from extended use of biomarker based therapy

2009 Revenues (million)	U.S.	France	Germany	Italy	Spain	UK	Japan	Total
Avastin (bevacizumab)	$2,894	$548	$275	$166	$219	$15	$360	**$4,477**
Rituxan/MabThera (rituximab)	$2,047	$269	$245	$180	$130	$118	$263	**$3,252**
Herceptin (trastuzumab)	$1,382	$331	$361	$267	$183	$185	$313	**$3,022**
Erbitux (cetuximab)	$697	$133	$102	$58	$91	$10	$133	**$1,224**
Total	**$7,020**	**$1,281**	**$983**	**$671**	**$623**	**$328**	**$1,069**	





source: Datamonitor, Company Annual Reports

Biomarker based therapy may increase or decrease treatment cost, the net effect is still under discussion, requiring in depth economic analysis

Reasons why personalized medicine and biomarker supported therapy could decrease cost

- Reduce waste/cost by use of appropriate treatment strategy for each patient (e.g. right dosing)
- No/reduced cost from treatment of non responder group
- Reduced rate of adverse events and treatment discontinuation will reduce unnecessary hospital admissions and outpatient healthcare contacts
- Improved treatment efficacy and effectiveness will improve productivity and reduce indirect healthcare cost

Reasons why personalized medicine and biomarker supported therapy could increase cost

- Combined use of diagnostic and treatment may result in an increase of drug treatment related cost
- Reduced patient pools may force industry to refinance development by charging substantial price premiums
- Prolonged survival of patients requiring care may lead to an increase in overall cost
- Development cost for given drug may increase due to extended development timelines

Underlying promise: Better targeted therapies and biomarkers will lead to an increase in effectiveness

What increase in cost is acceptable for what increase in effectiveness?

"Independent of the cost effectiveness, I can only spend money I have" – *Canadian (Ontario) health official*

Pharmaco-economic analysis combines cost and effect; cost effectiveness and cost utility analysis perceived as most relevant for stratified therapies

Study types	Characteristics	Costs considered	Effects considered
Cost minimization	• costs of different strategies are compared, while effects considered to be equal		-
Cost benefit	• effects are expressed in monetary terms		(monetary)
Cost effectiveness Cost utility	• effects are expressed in clinical or utility terms		

Limitations

- these methods rarely address the budgetary impact
- the relevance of "traditional" pharmacoeconomic outcome often remains unclear
- substantial variation between countries on use of assessment and resulting benefit

modified after Marshall et al. 2002

Cost and treatment effectiveness versus current standard of care will set the stage to decide on the value and funding of new therapies

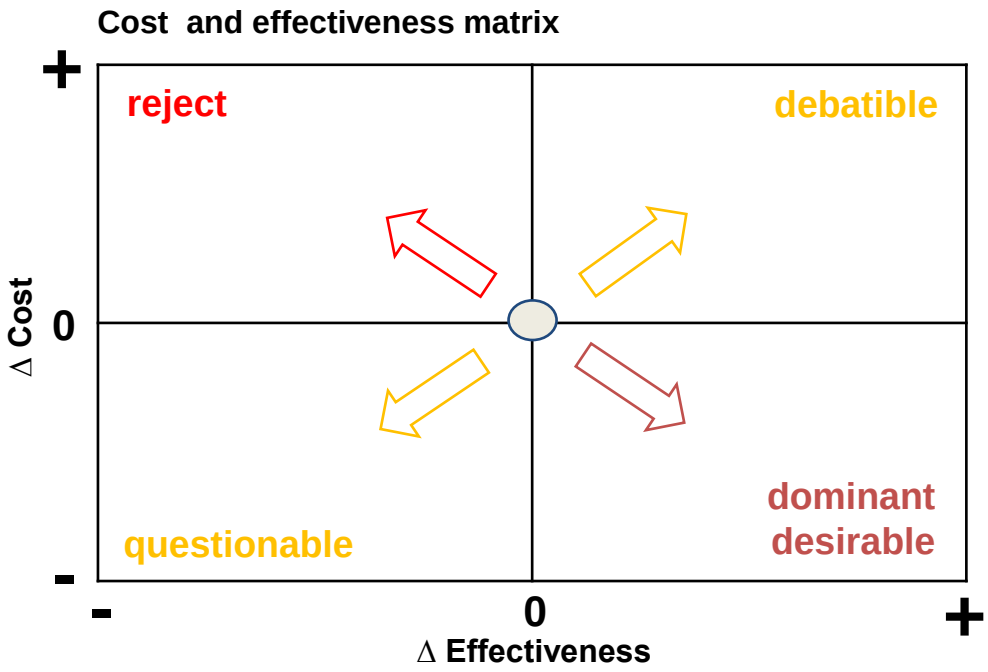
The promise of personalized medicine

To improve health care by:

- Increased treatment effectiveness
- Minimized treatment side effects
- Optimized timing, dosing and treatment duration

Realize saving potentials

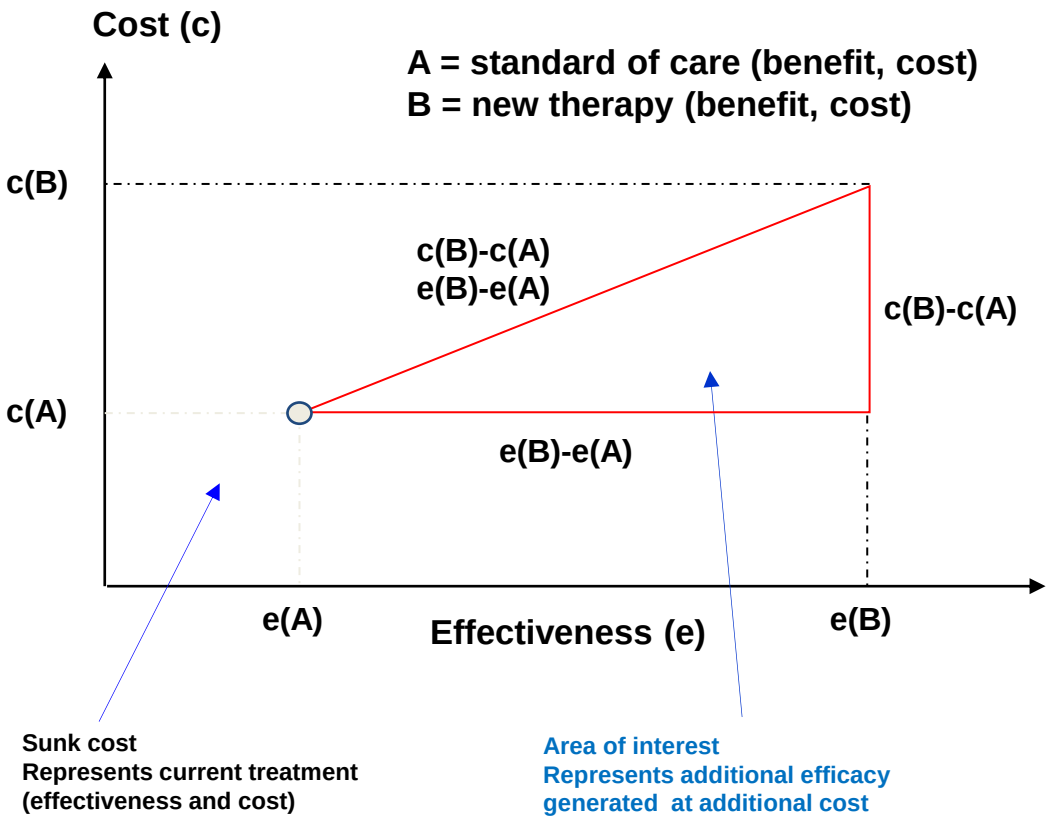
- Eliminate cost associated with treatment failure
- Eliminate cost associated with adverse events
- Eliminate cost due to unnecessary therapy



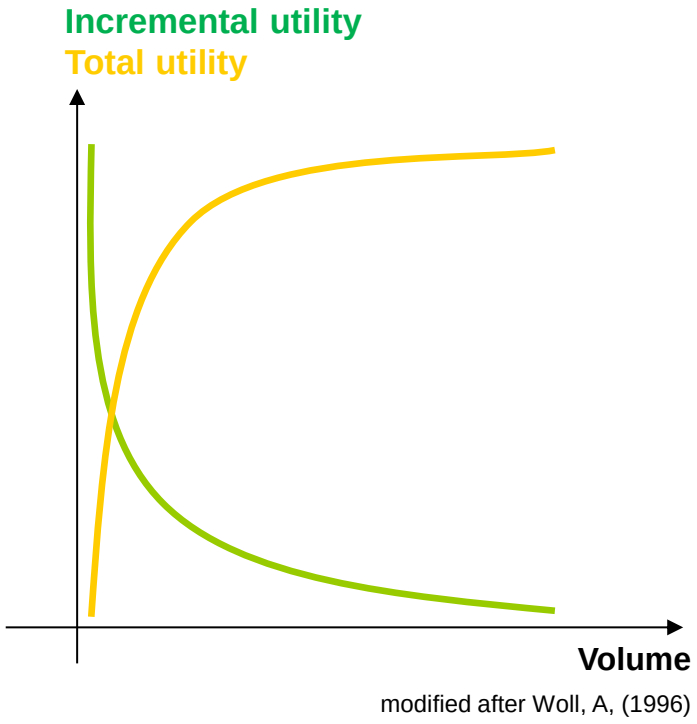
Combined assessment of cost and benefit required versus active comparator, no placebo

Application of the utility concept of micro-economic theory; payers are interested to understand the incremental change in benefit and cost of a new treatment versus standard of care

Incremental cost effectiveness

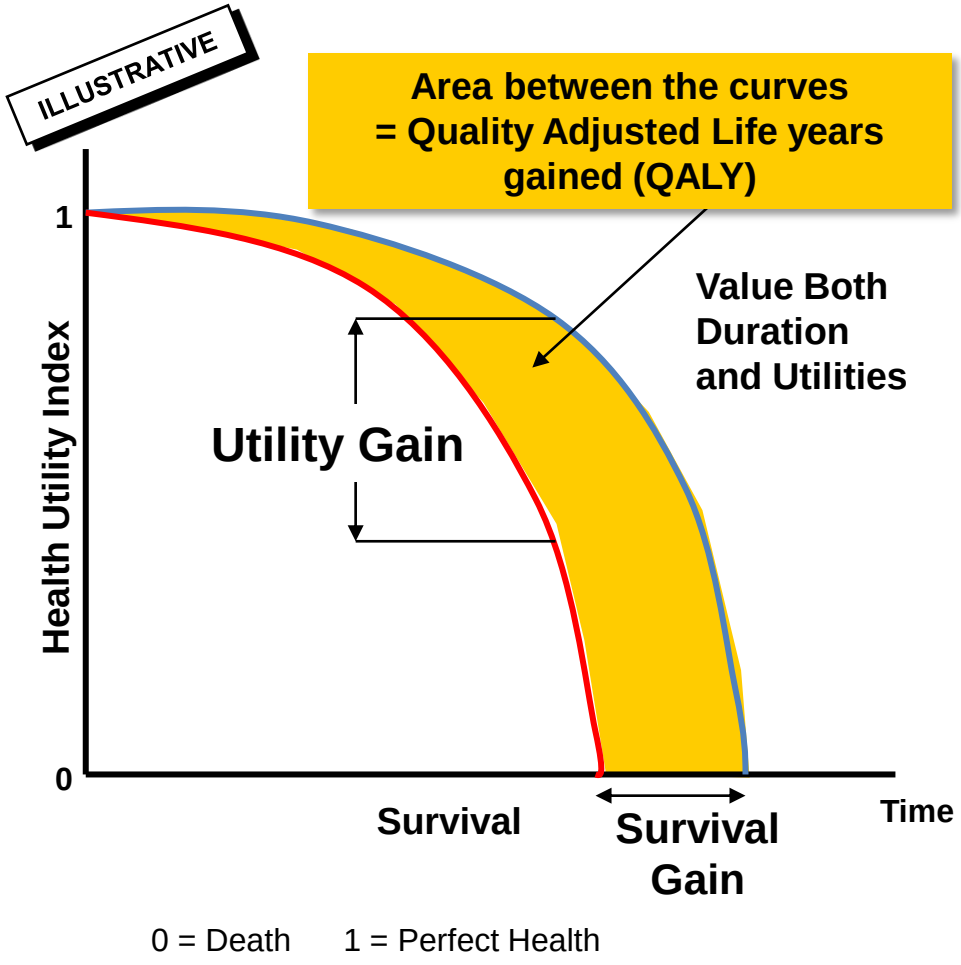


Law of diminishing return



modified after Woll, A, (1996)

Pharmaco-economic decision making is often based on quality adjusted life years gained (QALY); no difference is made whether the gain results from a gain in life years without improved utility or the other way around



Quality Adjusted Life Years (QALY)

- The QALY approach in pharmacoeconomics is rooted in the utility theory and allows for a value to be assigned to each life year of an individual
- Patients may benefit from medical interventions by
  - Improving their health status without gaining additional life years
  - By gaining life years without improving their health status
  - By a combination of both
- 1 QALY = 1 year of life at perfect health
- To determine the QALY benefit of new treatments, the cumulative QALY gain is calculated comparing alternative treatment outcomes with each other
- Representative QALY estimates for ESRD and kidney transplant patients from the literature:
  - ESRD, dialysis: 0.55
  - Patient after kidney transplantation: 0.70

Cost-effectiveness thresholds are often used to determine the reimbursement status and price point of new medical procedures

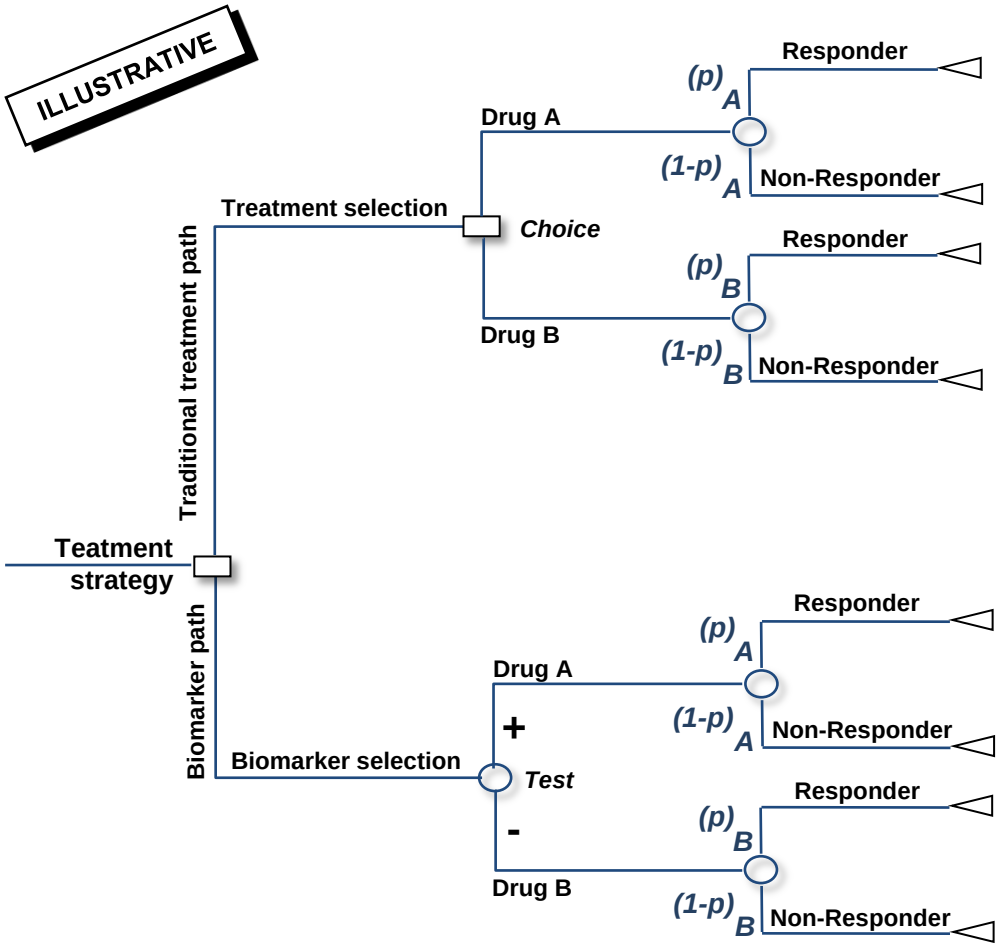
Example: UK cost-effectiveness decision criteria

<£20k per QALY	• **Cost effective**	**Typically recommended for unrestricted use**
£20-£30k per QALY	• **Borderline cost-effective,** • **limit guidance to patients which are particularly at risk**	**Typically recommended for restricted use**
>£30k per QALY	• **Generally not cost-effective**	**Typically rejected, except for cases without alternatives or with very limited budget impact**

- **"It is apparent that the appraisal committee has been reluctant to recommend the use of technologies with a cost effectiveness ratio of more than £ 30,000 [per QALY gained]."**

Michael Rawlings, Chairman NICE, cited in SCRIP

Decision tree and analytical requirements for an incremental analysis of cost and benefit of personalized medicine versus standard treatment



- **<u>Clinical and pharmaco-economic data needs for analysis and for use with payers</u>**

- Health outcomes data, morbidity, mortality (e.g. overall survival in oncology)
- Surrogate endpoints second best options (e.g. remission rate, progression free survival)
- Resource utilization
- Cost for each resource item
- Long term health outcomes data, resource utilization and cost
- Diagnostic test performance
- Number needed to treat (NNT)
- Health utility (QALY) and health related quality of life (HRQL)

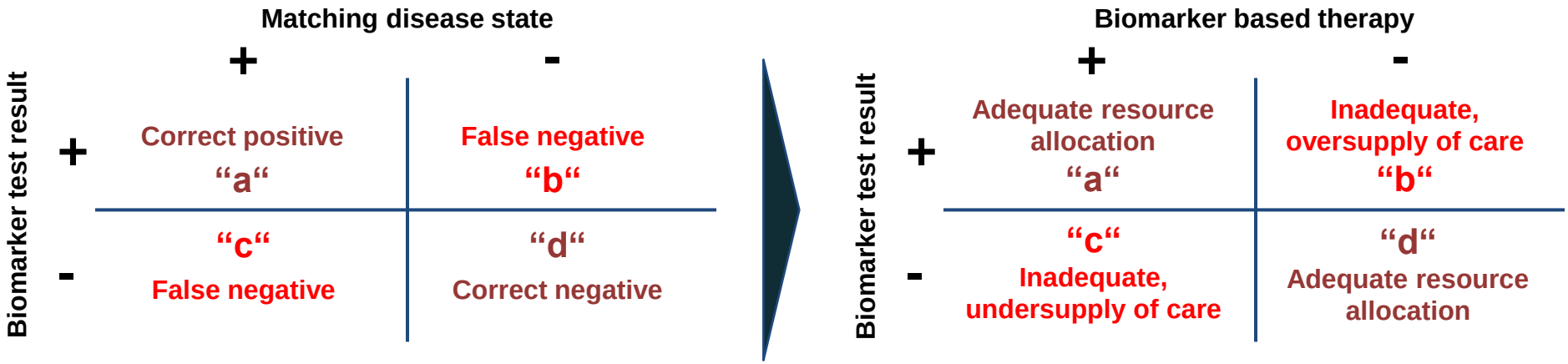
Comparative assessment of resource use, cost and health outcomes/benefit

Analysis done for each treatment arm

Incremental analysis of alternative treatment strategies

(Probabalistic) sensitivity analysis

Biomarker tests add additional complexity: sensitivity and specificity of biomarker tests may contribute to outcomes and cost of therapies



Sensitivity: a / (a+c)

Specificity: d / (b+d)

Positive predictive value: a / (a+b)

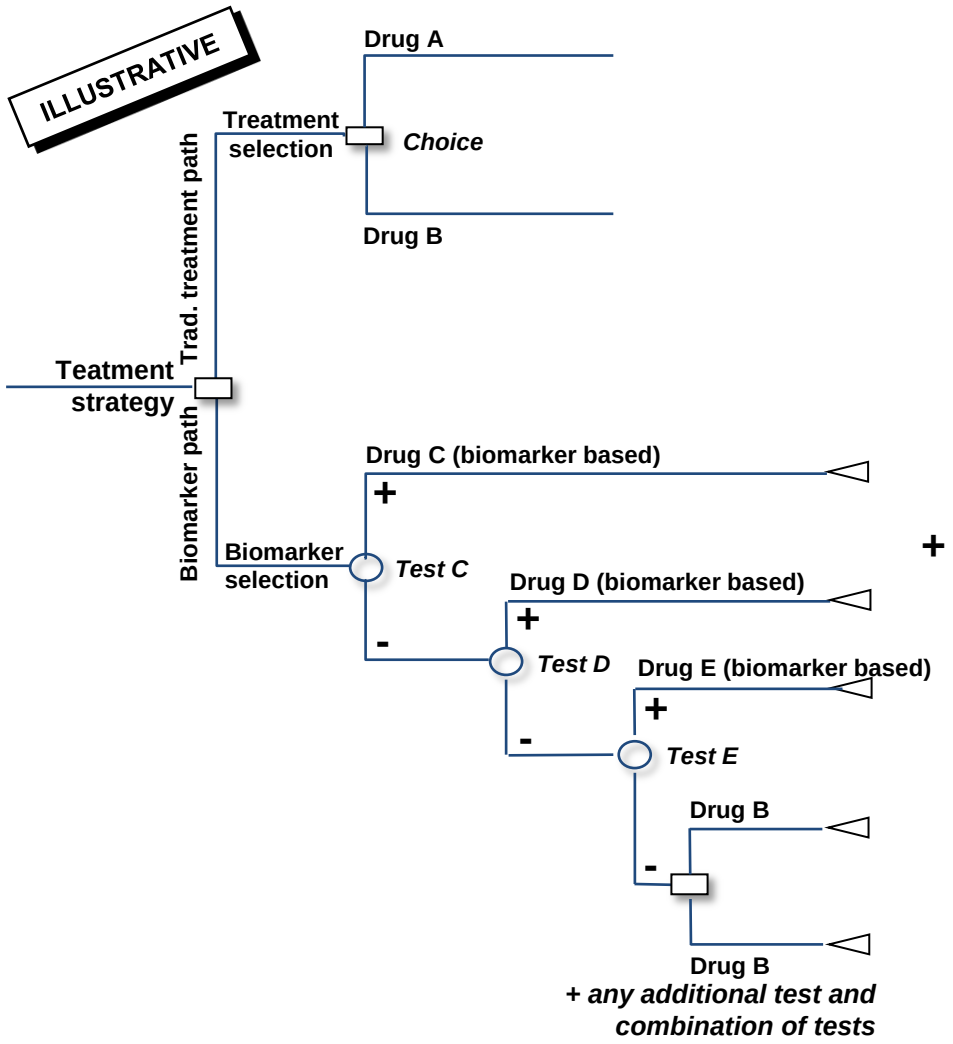
Negative predictive value: d / (c+d)

"b", "c" : inadequate resource and budget allocation

"b" : inappropriate use of a potentially very expensive therapy

"c": an efficacious treatment is withheld from patients, potentially causing an increase in downstream cost

Sequential application of biomarker tests would allow an increasing number of patients to benefit from biomarker based therapies; risk of excessive cost due to slicing and orphanizing of target population



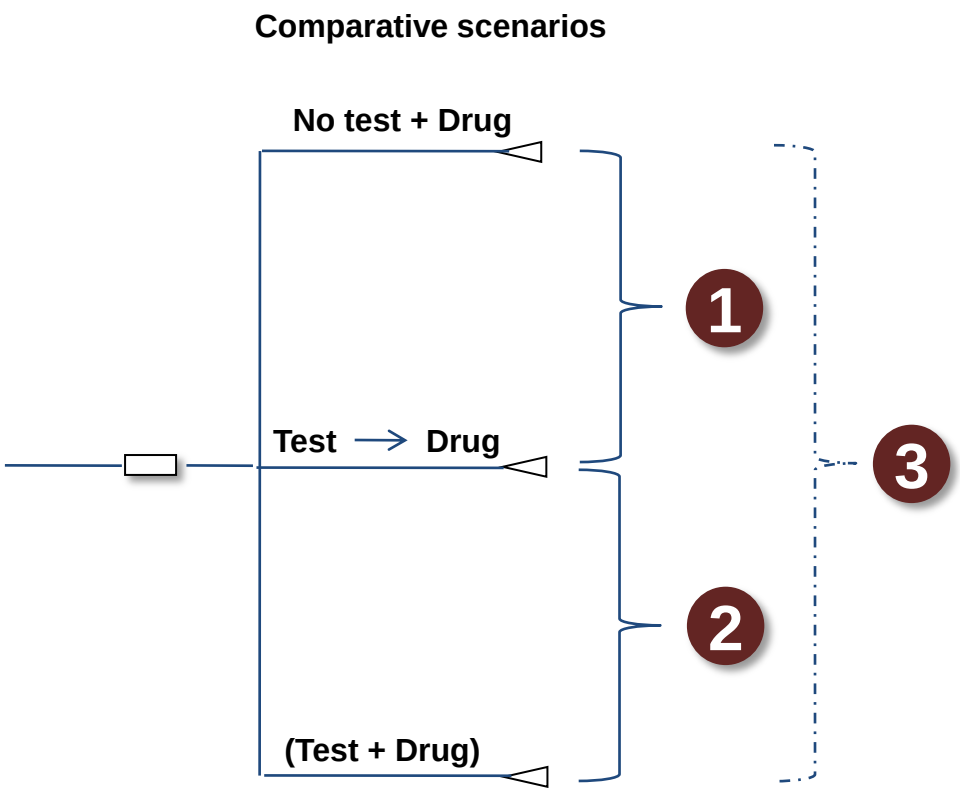
In common adult tumors—such as pancreatic, colorectal, breast, and brain cancers—the number of mutated driver genes is often three to six, but several tumors have only one or two driver gene mutations (Fig. 5). How can this be ex-

source: Vogelstein et.al. (2013)

- Efficacious and safe biologic treatment options for use in defined, often small patient subgroups, characterized by biomarker tests.

- Remaining “non responder” to biomarker tests to receive standard therapy?

Possible comparative scenarios for clinical and pharmaco-economic analysis of pharmacogenetic testing and companion diagnostic



- Goal **1**: Investigate the cost effectiveness of genetic testing strategy versus no testing strategy

  Competition between pharmaco-genomic test and traditional treatment practice

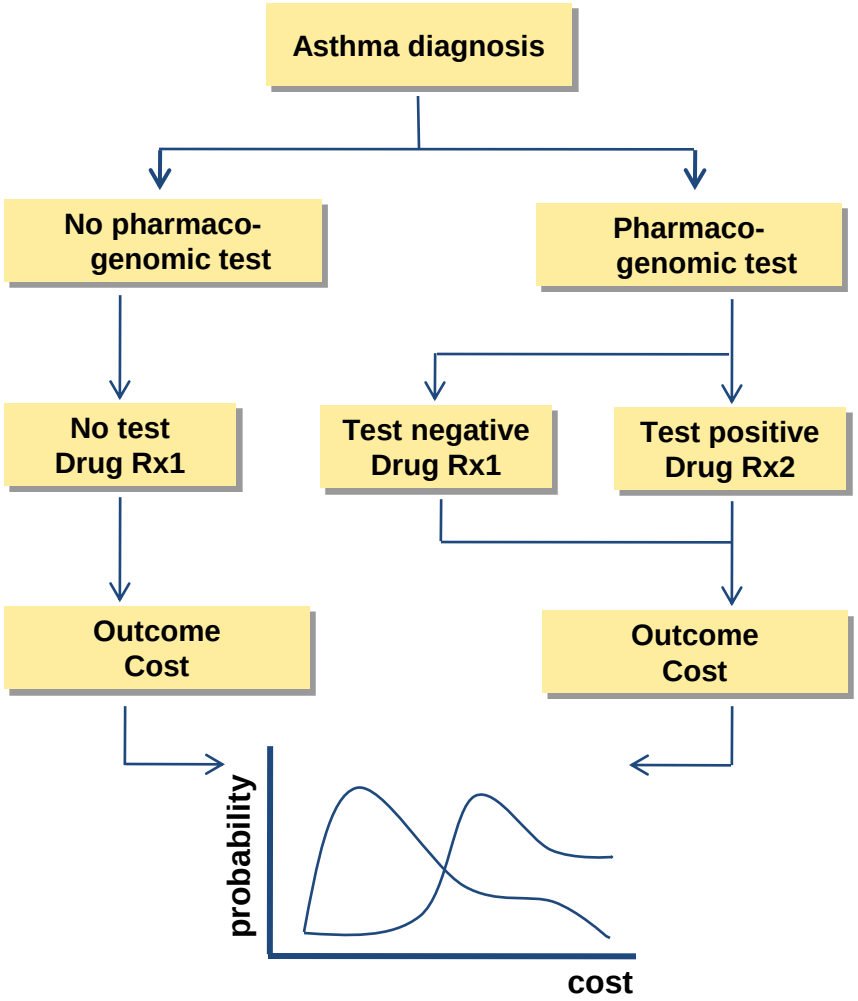
- Goal **2**: Investigate the cost effectiveness genetic testing strategy versus companion diagnostic strategy

  Competition between cost-effective pharmacogenomic test and new companion diagnostic approach

- Goal **3**: Investigate the cost effectiveness of no testing strategy versus companion diagnostic strategy

  Only of relevance if analysis “1” confirms that no-testing strategy is cost effective over testing strategy

Case study: economic framework of hypothetical pharmaco-genomic asthma test to investigate the cost and outcomes of therapeutic interventions

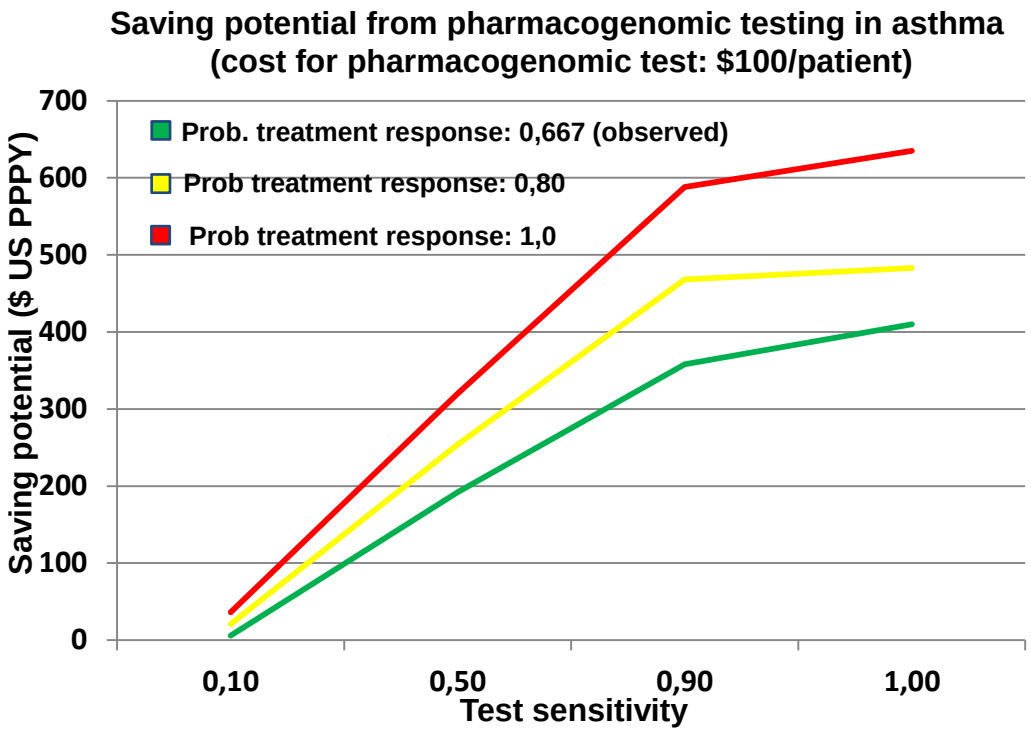


source: modified after Stallings et.al. (2004)

Model assumptions

- Assumption: Availability of pharmacogenomic test to detect responder/non-responder to available asthma therapy
- Research question: to compare the health care cost of an observed treatment protocol (base case) with those in hypothetical treatment scenarios
- Data basis: 28.324 asthma patients; claims data
- Type of analysis: retrospective data analysis
- 66,7% of patients classified as responders
- Cost responder: $3.140; cost non-responder: $5.132
- Probability of asthma related emergency visit: 0,4% in responder group and 0,6% in non-responder group
- Cost for pharmacogenomic test varied from $100 to $300

Modeling outcome confirms the saving potential of the hypothetical pharmaco-genomic asthma test



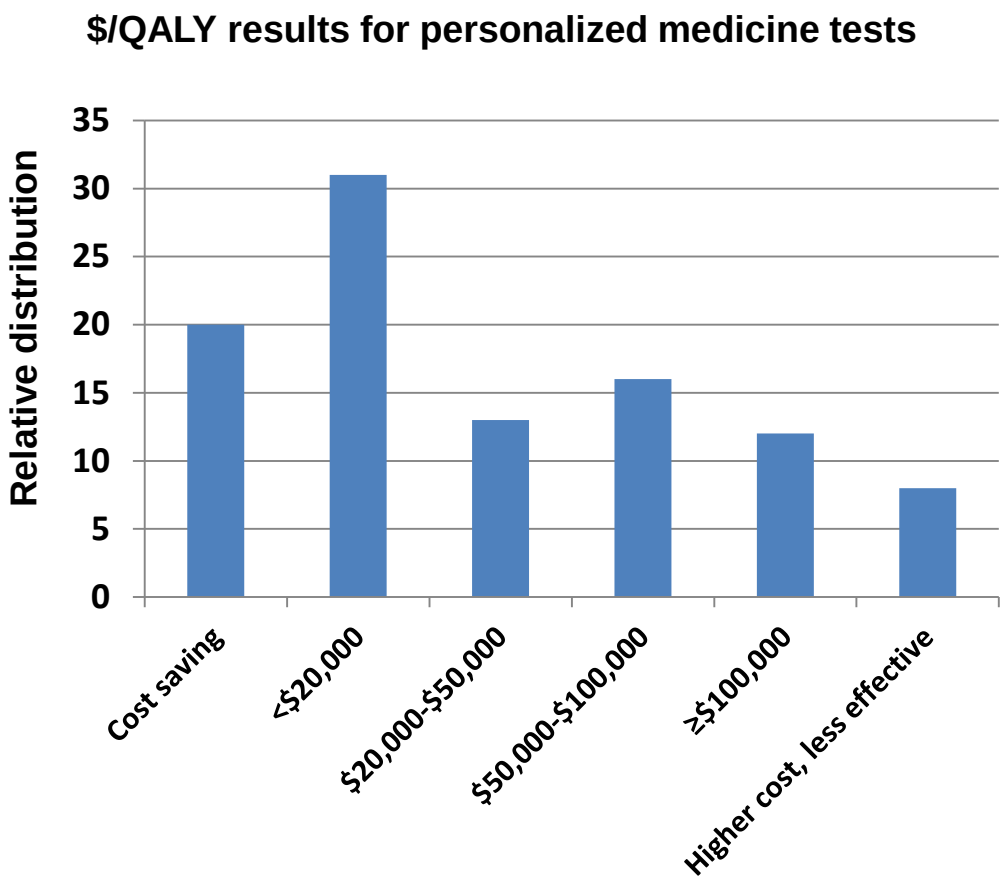
Saving potential	Test sensitivity			
Prob. treatment response	1,0	0,9	0,5	0,1
0,67	$410	$358	$192	$6
0,70	$452	$393	$198	$2
0,80	$483	$468	$254	$21
0,90	$588	$515	$283	$48
1,0	$635	$589	$320	$36

Interpretation

- Most favorable case, test sensitivity of 100% and unchanged treatment effectiveness results in saving of $410/patient
- If combined with more effective treatments, the saving potential could increase to a max.of $635/patient
- At 1,0 test sensitivity and 1,0 effectiveness probability a test could cost up to $700 to generate ~$410/patient

source: modified after Stallings et.al. (2004)

Available data from 59 economic assessments of personalized medicine tests confirms supportive cost utility results in majority of cases and



- Total of 59 published cost utility studies identified.

- 20% cost saving
- 60% cost effective
- 20% not supported by CUA

- Low number of CUA studies (n=59) reflects limited demand for data on diagnostic tests.
- Payers feel uncertain about value and application of personalized medicine tests.
- Delayed reimbursement of personalized medicine tests reflects payer uncertainty.

source: Phillips et al (2014)

Variability of cost effectiveness results also restricts the fast and general application and reimbursement of biomarker tests in clinical practice

Summary of results of cost utility and cost effectiveness studies; selected examples

Study	Test and intervention	Result
Eckman et.al. (2009)	Test for CYP2C9 and VKOBC1 variants and genotype-guided warfarin dosing in nonvalvular AF	$170.000 per QALY.
Meckley et.al. (2009)	Genotype (CYP2C9 and VKORC1)-guided warfarin dosing in AF patients	$60.725 per QALY
Patrick et.al. (2009)	Genotype (CYP2C9 and VKORC1)-guided warfarin dosing in AF patients	$50.000 - $100.000 per QALY
Leey et.al. (2009)	CYP2C9 genotyping in acenocoumarol tx	€4.233 per bleeding event avoided
You et.al. (2004)	CYP2C9 genotype-guided warfarin dosing	$5.778 per major bleeding averted

source: modified after Wong WB et.al. (2010), Klang et.al. (2010)

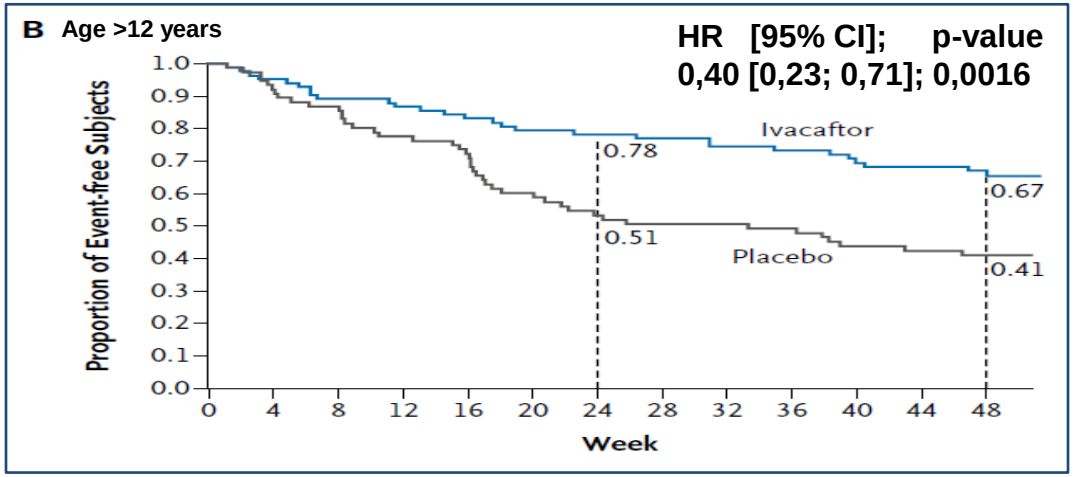
Case study: Ivacaftor (Kalydeco®) offers substantial clinical benefit for 2.2% of CF patients with G551D-CFTR mutation

Indication:	Cystic fibrosis (CF)
Drug:	Ivacaftor (Kalydeco®)
Biomarker:	G551D-CFTR mutation
Orphan status	yes

CF mutations and frequency

Type of mutation	Freqency
Δ F508	69,4%
unknown	15,7%
G542X	2,3%
G551D-CFTR	2,2%
Δ I503	1,6%
W1282X	1,4%
N1303V	1,2%
18 other mutations	5,9%

source: MCKone et al. (2003)



source: Ramsey et al. (2011); G-BA (2013) Therapy recommendation (Therapie Richtlinie) Kalydeco®

	Placebo (N = 78)	Ivacaftor (N = 83)	Difference [95% CI]	p-value
Lung function (% FEV1 predicted); week 24	**- 0,18%**	**10,39%**	**10,58% [8,57; 12,59]**	**< 0,001**

source: G-BA (2013) Therapy recommendation (Therapie Richtlinie) Kalydeco®

High cost of Ivacaftor (Kalydeco®) drive mixed outcomes of payer assessments in Germany and Scotland

Germany: Additional benefit assessment according to § 35a SGB V and § 130b SGB V rebate agreement

Additional benefit assessment (§ 35a SGB V)	
Children 6 – 11 years (N = 27)	minor
Adolescents, adults >12 years (N = 143)	substantial
Therapy, comparative therapy and cost	
Comparative therapy	Best supportive care
Annual cost comparative therapy	€ 12,671.67
Annual cost Kalydeco®	€ 289,351.65
Cost test G551D-CFTR	€ 557,59
Rebate agreed with GKV-SV (§ 130b SGB V)	
Rebate agreed with GKV-SV (% of initial manufacturer selling price	~€ 36.350 (~13,50%)

source: Vertex (2012) Additional benefit assessment Kalydeco®, Modul 3 and Modul 4; Lauer Taxe Kalydeco®

Scotland: Assessment of cost effectiveness and recommendation for use of Kalydeco with NHS Scotland

Comparative clinical effectiveness	
Modeling concludes on mean survival benefit of 17.8 years, up from 16.1 to 34.0 years	
Substantial uncertainty on modeling approach as no data beyond 48 weeks of treatment was available	
Pharmaco-economic assessment	
Incremental QALYs	5.40
Incremental cost	£ 1,780,591
ICER (£/QALY)	£ 330,657
SMC recommendation	
Ivacaftor (Kalydeco®) is not recommended for use within NHS Scotland	
The submitting company's justification of the treatment's cost in relation to its health benefits was not sufficient to gain acceptance by SMC and in addition the company did not present a sufficiently robust economic analysis to gain acceptance by SMC.	
£21m "orphan drug" fund available to improve access to Kalydeco® for eligable patients	

source: NHS Scotland 2012

Payers and budget holders feel unclear about the growing number of variables and analytical complexity of biomarker based therapy

Payer uncertainty related to features of biomarker based treatments

- Trial design
- Comparative therapy
- Efficacy versus effectiveness
- Evidence basis
- Sustainability of response
- Reproducability of results
- Slicing and orphanizing of indications
- Long term treatment cost

- The substantially increased number of variables and treatment scenarios will force decision maker to adjust established decision criteria
- Potential disconnect between high target price of biomarker based therapy based upon short term data
- Biomarker tests are defined treatment components that require a separate assessment independent of related pharmaco-therapy

Effectiveness data is preferred by payers for budgetary decision making, risk sharing agreements are often applied to address unclear data quality and relevance of evidence

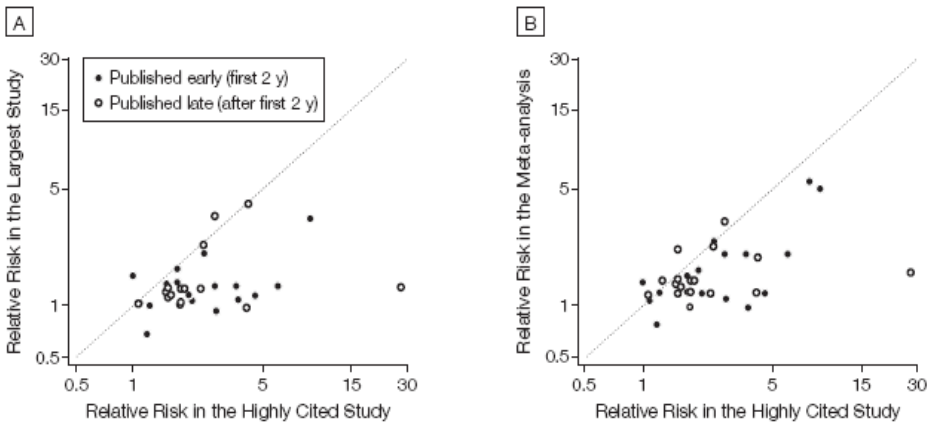
Efficacy

- Indicates a therapeutic effect in a controlled research environment
- Used by regulatory environment
- Available at launch of product

Effectiveness

- Indicates a therapeutic effect in normal clinical practice
- Desired by payers for budget decisions
- Not available at launch of product

Figure. Relative Risks in the Highly Cited Studies vs the Corresponding Largest Studies and in the Highly Cited Studies vs the Corresponding Meta-analyses



Diagonal lines represent equal effects between the highly cited study and the largest study (A) or the meta-analysis (B), respectively. A, Not shown are 3 topics whereby the highly cited study was the same as the largest study. B, Meta-analyses may include the data from the highly cited studies, but the latter are usually small compared with the corresponding meta-analyses (median, 5%; interquartile range, 2%-12%, of the meta-analysis sample size).

source: Ioannidis & Panagiotou (2011)

Case study Evidence Basis

- Payers are uncertain about the relevance of efficacy data for daily clinical decision making
- Recent meta analysis on biomarkers indicated that effect size of highly cited studies may vary substantially from subsequent study results
- Risk that favorable product profile can not be reproduced in clinical practice which may lead to substantial budget risk

Risk sharing agreement
Conditional reimbursement

Innovative price and reimbursement arrangements may allow payers to address the budgetary risk from unclear data situation

Financial utilization models	• **Price – volume agreements** • **Dynamic benefit agreements (rebates depending on market share targets)** • **Patient capitation and dose caps**
Outcomes based models	• **Different reimbursed price depending on patient outcomes** ➢ **Treatment response** ➢ **Treatment outcome**
Risk based models	• **Different reimbursed price depending on patient subgroups by** ➢ **Indication** ➢ **Treatment history** ➢ **Risk factors**

source: modified after Grüger J (2009); ISPOR

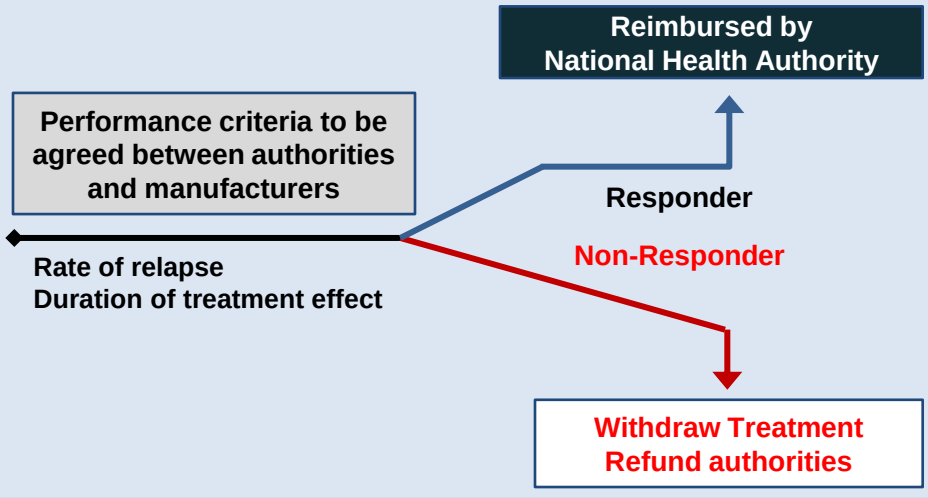
There are two principal risk-sharing schemes employed, performance-based risk-sharing schemes or financial-based risk-sharing schemes

Principle Types of Risk-Sharing Agreements

Performance Based

Performance-Based Risk-Sharing Schemes

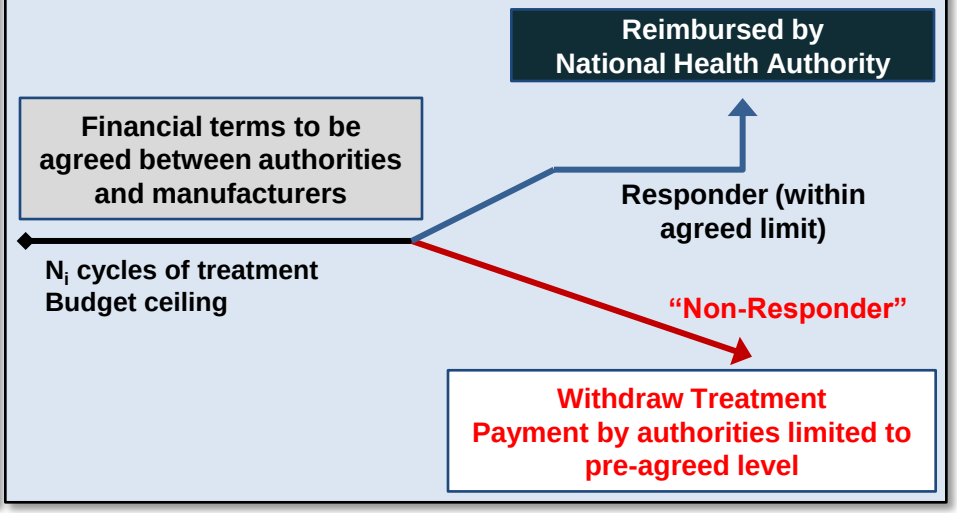
- Companies refund drug costs or provide free drug if desired outcome is not achieved
- If therapeutic efficacy is not optimal, may result in a price cut or withdrawal of the treatment



Financial Based

Financial-Based Risk-Sharing Schemes

- Include price-volume agreements, fixed payment and patient access schemes
  - Price-volume agreements focus on controlling financial expenditure associated with prescribing the drug; pharma companies provide refunds when treatment continues after the set budget is exceeded
  - Patient access schemes provide free or discount drugs for an agreed period of time



Risk-sharing agreements in place across the EU5 for different cancer therapies; examples from two countries

	Company	Drug	Indication	Agreement Type	Strategy
	**Celgene**	**Revlimid**	Multiple Myeloma	Financial	• The NHS pays for treatment for the first 2 Years, if treatment is required after the 2 years, then Celgene will cover the costs
	Astra-Zeneca	**Iressa**	Non small cell lung cancer (NSCLC)	Financial	• NHS buys Iressa at fixed cost of £12.200 irrespective of the duration of the treatment. NHS pays for the required EGFR test
	GSK	**Votrient**	Advanced Renal Cell Carcinoma	Financial	• 12.5% discount off the list price and will pay the NHS a rebate depending on the outcome of a head-to-head trial known as COMPARZ, data of which will be available in 2012
	**Merck KGaA**	**Erbitux**	Advanced or Metastatic CRC	Performance	• Erbitux should only be used on patients who test positive to EGF with the wild type KRAS gene; the company is required to pay 50% of the costs of the drug in the event that doctors see no stabilization of a patient's metastatic tumor after 2 months
	BMS	**Sprycel**	CML and ALL	Performance	• The Italian health service fully covers the cost for responders; manufacturers refund the cost in the case of disease progression
	GSK	**Tyverb**	HER2+ Breast Cancer	Performance	• The Italian health service fully covers the cost for responders; manufacturers refund the cost in the case of disease progression
	**Genentech**	**Avastin**	NSCLC, CRC	Financial	• $55.000 expenditure ceiling for all patients agreed with Medicare. Covers all agreed indications
	Genomic Health	**Oncotype**	Breast Cancer	Financial	• Conditional reimbursement approval with United Health for limited period of time to assess efficacy

source: nterviews and analysis; IHS Global Insight (2011)

Summary

- Personalized medicine is an attractive treatment concept that will have a substantial impact on cost and benefit of pharmaceutical treatments in the future
- Pharmaco-economic analysis of personalized medicine is not different from economic analysis of conventional treatments but substantially more complex
- Convincing health outcomes data and pharmaco-economic data is needed to confirm the clinical and economic value of personalized medicine to clinicians, payers and patients
- To control cost payers will exploit contracting and payment for performance in order to address potential budget uncertainty and to split cost and risk between stakeholders
- Whether personalized medicine will eventually increase or decrease spending is unclear due to the small number of outcomes studies available and lack of long term data
- The current concepts are best described as biomarker based stratified therapy. Truely individualized therapy will further complicate the economic and clinical case and create new competetive scenarios and analytical challenges

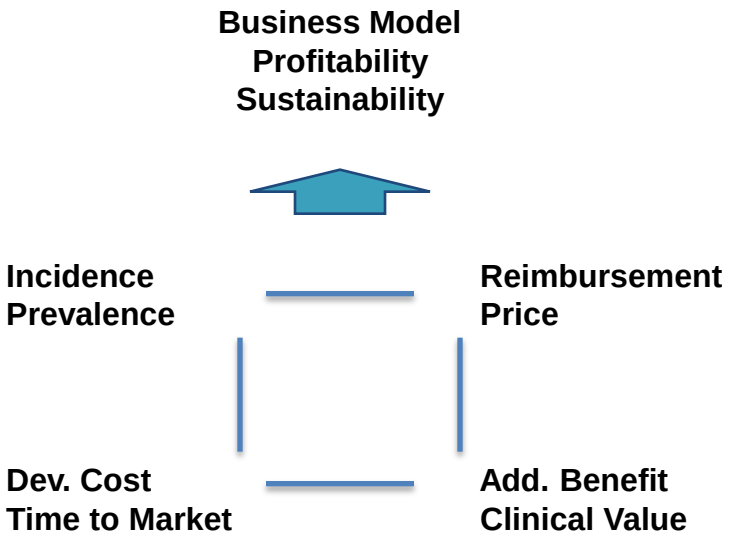
Multiple factors and decision criteria apply to drive the cost-effectiveness and commercial attractiveness of biomakers and stratified therapies

Category	Factors to assess	Expressions that favors cost effectiveness and acceptance
Genotyping	Prevalence	high prevalence of allele in target population
	Penetrance	high penetrance
Disease	Prevalence	high prevalence in target population
	Unmet need	high unmet need (e.g. mortality, mortality)
	Economic impact	high direct cost, high indirect cost
Biomarker test	Sensitivity	high sensitivity
	Specificity	high selectivity
	Cost	low or moderate cost
Treatment	Efficacy	significant, clinicially relevant and sustainable
	Safety	reduction in adverse event that impact cost
	Cost	low or moderate cost
Comparative therapy	Efficacy	low, not relevant
	Safety	frequent adverse events
	Cost	moderate or high cost

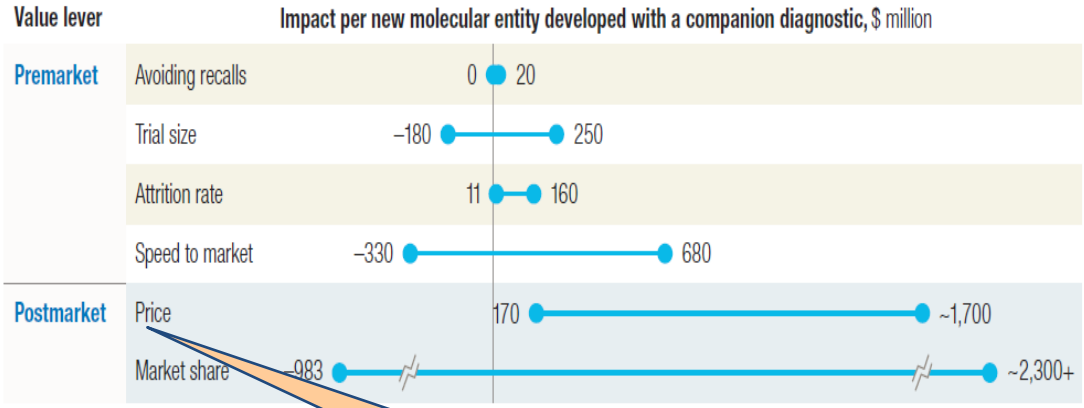
(selected categories and factors only)

source: modified after Veenstra (2012)

Price and market share are considered to drive the commercial aspiration of personalized medicine, clearly exceeding the impact of potential savings and accelerated time to market



Sensitivity analysis and impact of selected business attributes on expected commercial value



[1]Based on case examples and expert interviews.

source: modified after Davis et al. (2010)

"Ultimately, payers will determine the fate of personalized medicine. Money will follow value. Up to now, it is too early to conclude on the value of personalized medicine"

Payer, Canada

As personalized medicine aims to fulfills its promise, affordability becomes the key issue that may lead to less attractive cost – effectiveness ratios

Personalized medicine to replace traditional pharmaco-therapy

Rx1

Biomarker
Personalized
Individualized

Rx1 **Rx2** **Rx3**

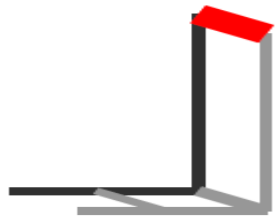
Increased effectiveness and safety
Gradually evolving individualization

Budget available

Budget available unchanged

Clinical and economic threshold "exchange rate"

£30.000/QALY

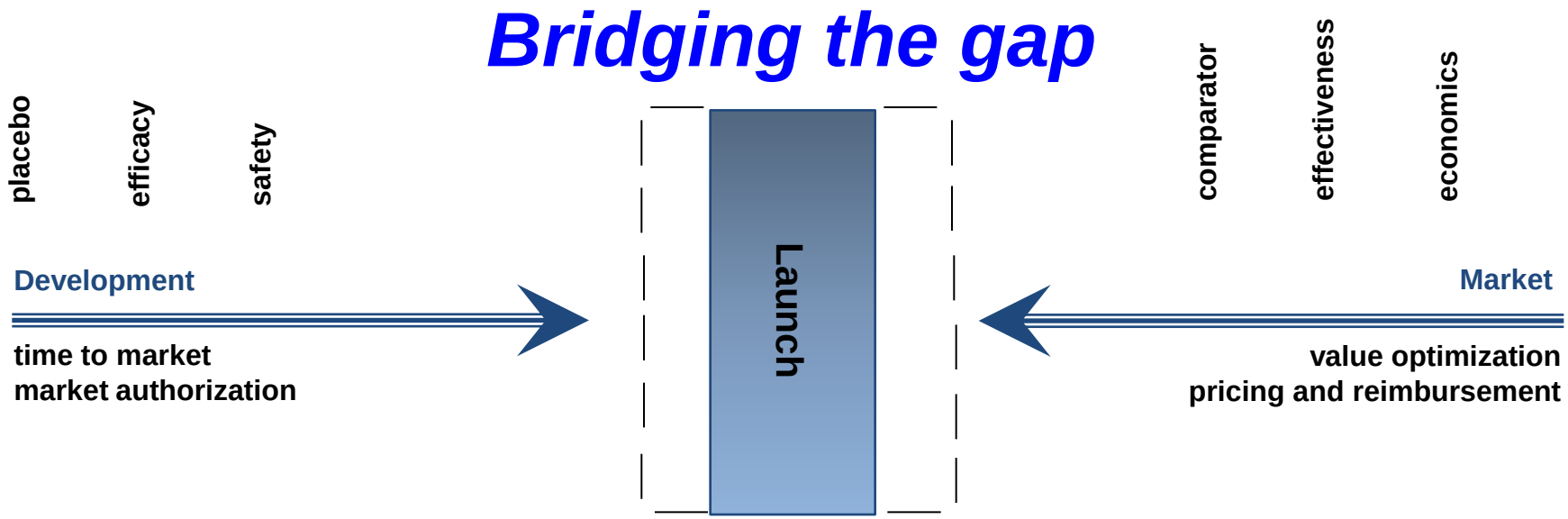


£10.000/QALY ?

Commercial success of personalized development will depend on smooth integration of clinical and commercial requirements on product development

Realize sustainable and optimal return on investment by means of:

- Reduced time to market by targeted drug development
- Unrestricted reimbursement at optimal price, reflecting the true value



As personalized medicine is not limited to pharmaceuticals, competition for fundings across healthcare sectors will intensify

Definition of personalized medicine

- Any of the way in which understanding meaningful differences between individuals helps guide the use and interpretation of diagnostics as well as choices in therapies and prevention

- Pharmaceuticals; “biologics”
- Biomarker

- Tissue grafts
- Stem cell therapy
- Other individualized therapies

- Surgery
- Devices
- Delivery of care

- **Individualization not limited to biomarkers and pharmacotherapy**
- **Individualized approaches increasingly in competition with biomarker based pharmacotherapy**
- **Affordability of individualized approaches and priorities to be determined**

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