



### The Economics of Personalised Medicine

Economic opportunities and threats facing personalised medicine

- Dr Richard Barker, The Oxford Centre for Accelerating Medical Innovations

What are some of the issues from the payer perspective?

- Dr Rob Epstein, Medco

What are challenges for suppliers trying to generate evidence?

- Prof Adrian Towse, Office of Health Economics

Chair

- Rob Thwaites, United BioSource Corporation

**UBC**  
United BioSource Corporation  
Evidence Matters™

## Economic opportunities and threats facing personalised medicine

Dr Richard Barker  
Director, CAMI  
ISPOR Symposium  
November 2011

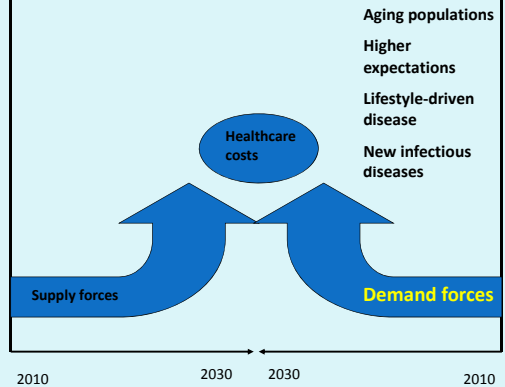
## Personal background + lessons

- McKinsey consultant
- Chiron Dx CEO
- iKnowMed CEO
- Molecular Staging CEO
- Director General ABPI
- Economics rule OK
- Rx and Dx economics ▲
- Cancer a fruitful field
- Pharmacos cautious
- Governments supportive
- Payers expect lower cost
- Regulators unready
- Physicians ill-informed
- Technology not the limiting factor

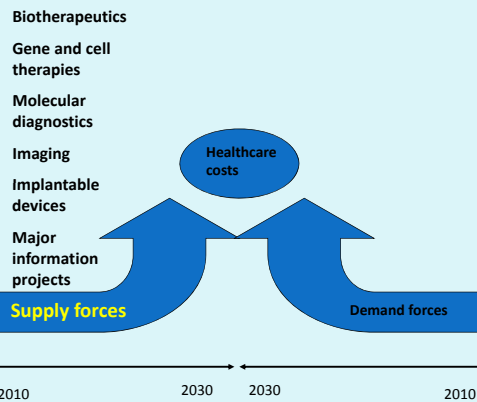
## Key messages

- Supply and demand creating a potential meltdown of health systems
- Personalised medicine prospectively part of the solution
- Focused development of new medicines will improve R&D productivity and affordability
- But we need to find the customer to whom to make the economic case

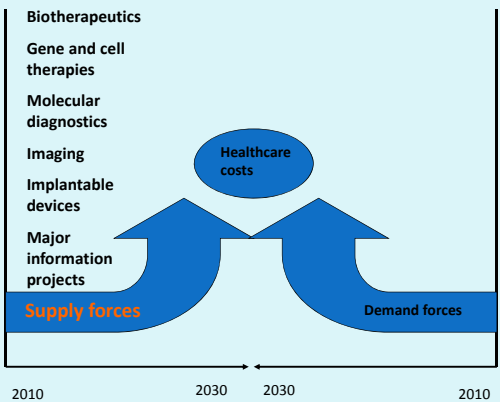
## Several powerful demand drivers

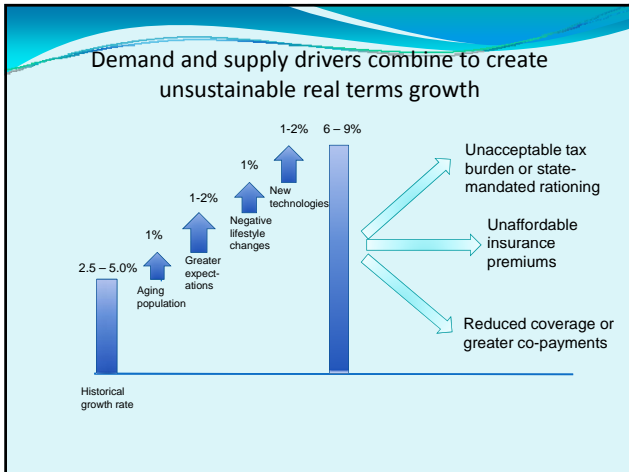


## Supply of new technologies also adds to healthcare costs



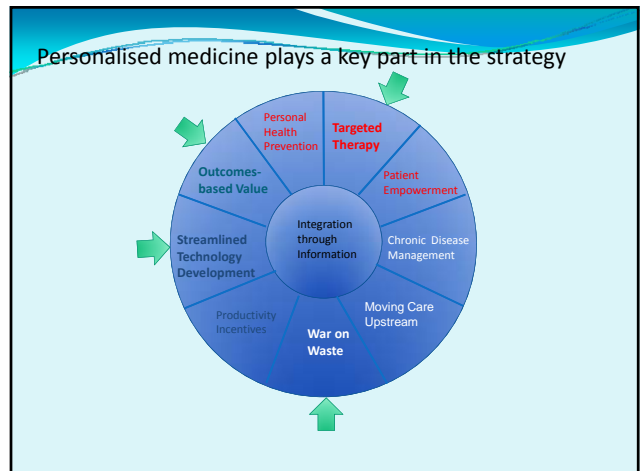
## Supply of new technologies also adds to healthcare costs





### We need a strategy to avoid the meltdown

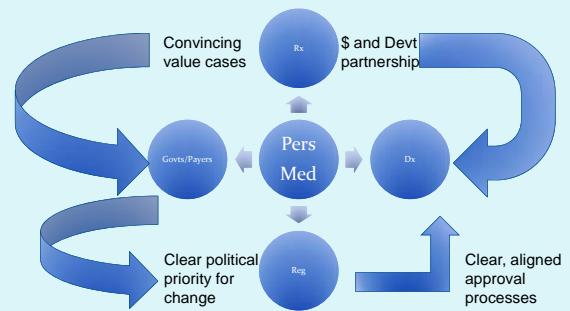
[www.2030healthfutures.com](http://www.2030healthfutures.com)



## But there are major barriers

- Real efficacy biomarkers often emerge after expensive development stages, rather than before them
- Validation still an unclear and expensive process, with funding limited
- Rx and Dx regulation are still separate processes
- Pharma companies still competing rather than collaborating to create standard markers
- Economics only beginning to be understood in HTA: eg differential efficacy: step pricing or average?
- Health systems not geared up to Rx-Dx offerings

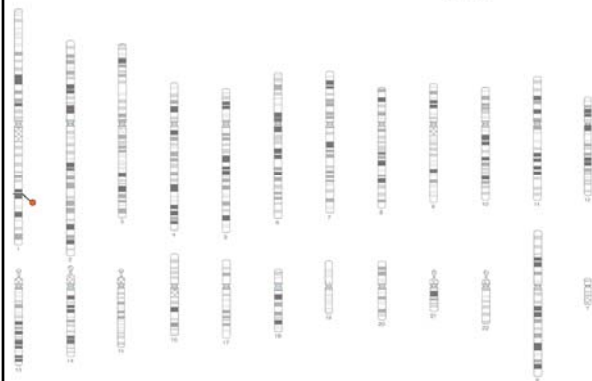
## And the economic ecosystem is rather complex ...

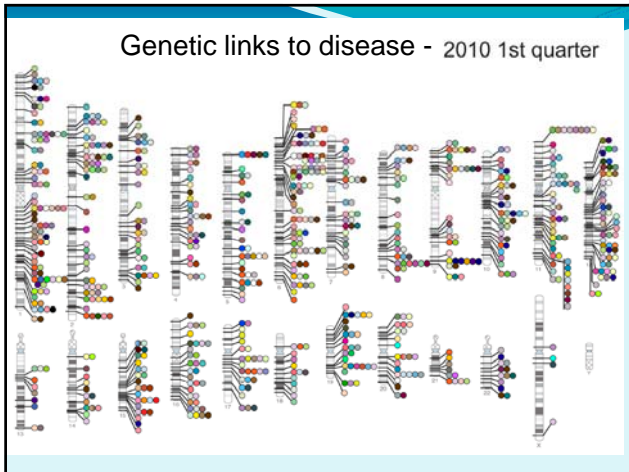


## The science is racing ahead of the economics...

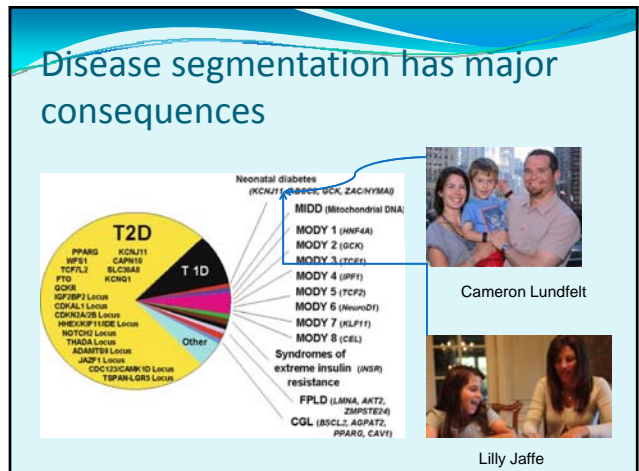
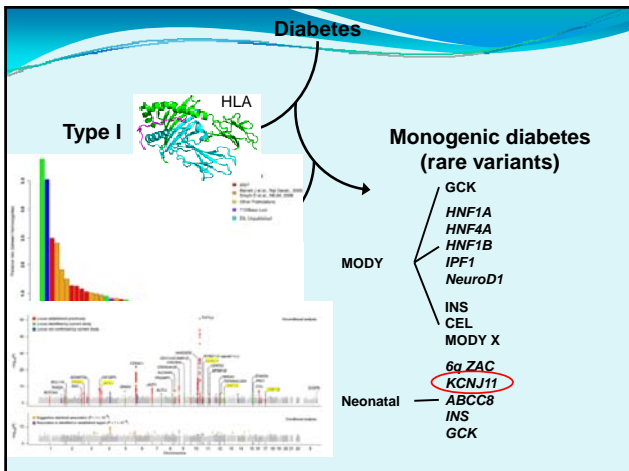
- Genome-wide association studies and other molecular and systems biology tools are redefining diseases
- Common diseases will segment by molecular basis
- Patient phenotypes will further complicate the picture
- Biomarkers will make increasing impact
- Physicians will want to respond, for the benefit of patients
- But most health systems will see “expensive” diagnostics and therapeutics rather than enhanced treatment outcomes/costs

## Genetic links to disease - 2005

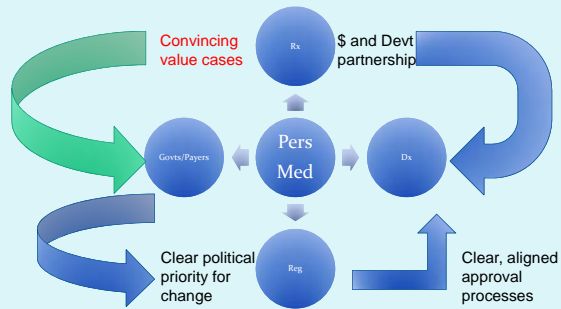




- ### Diseases and Traits with Published GWA Studies
- Macular Degeneration
  - Exfoliation Glaucoma
  - Lung Cancer
  - Prostate Cancer
  - Breast Cancer
  - Colorectal Cancer
  - Bladder Cancer
  - Neuroblastoma
  - Melanoma
  - *TP53* Cancer Predispos'n
  - Chr. Lymph. Leukemia
  - Inflamm. Bowel Disease
  - Celiac Disease
  - Gallstones
  - Irritable Bowel Syndrome
  - QT Prolongation
  - Coronary Disease
  - Coronary Spasm
  - Atrial Fibrillation/Flutter
  - Stroke
  - Subarachnoid Hemorrhage
  - Intracranial Aneurysm
  - Hypertension
  - Hypt. Diuretic Response
  - Peripheral Artery Disease
  - Lipids and Lipoproteins
  - Warfarin Dosing
  - Ximelegatran Adv. Resp.
  - Parkinson Disease
  - Amyotrophic Lat. Sclerosis
  - Multiple Sclerosis
  - MS Interferon-β Response
  - Prog. Supranuclear Palsy
  - Alzheimer's Disease in ε4+
  - Cognitive Ability
  - Memory
  - Hearing
  - Restless Legs Syndrome
  - Nicotine Dependence
  - Methamphetamine Depend.
  - Neuroticism
  - Schizophrenia
  - Sz. Iloperidone Response
  - Bipolar Disorder
  - Family Chaos
  - Narcolepsy
  - Attention Deficit Hyperactivity
  - Personality Traits
  - Rheumatoid Arthritis
  - RA Anti-TNF Response
  - Syst. Lupus Erythematosus
  - Sarcoidosis
  - Pulmonary Fibrosis
  - Psoriasis
  - HIV Viral Setpoint
  - Childhood Asthma
  - Type 1 Diabetes
  - Type 2 Diabetes
  - Diabetic Nephropathy
  - End-St. Renal Disease
  - Obesity, BMI, Waist, IR
  - Height
  - Osteoporosis
  - Osteoarthritis
  - Male Pattern Baldness
  - F-Cell Distribution
  - Fetal Hgb Levels
  - C-Reactive Protein
  - ICAM-1
  - Total IgE Levels
  - Uric Acid Levels, Gout
  - Protein Levels
  - Vitamin B12 Levels
  - Recombination Rate
  - Pigmentation



## The value case is key – but to whom is it to be made?



## Personal perspective

- Pharma companies must realise that their chance of reimbursement rests on tight definition of target population
- They need to pay for the trials that validate the marker and demonstrate the clinical and value case
- The Dx will need to be bundled with the Rx, so that diagnostics labs see no/little additional \$ burden
- This is part of the new industry paradigm critical for industry's survival

## The Oxford Centre for Accelerating Medical Innovations (CAMI)



## Centre for Accelerating Medical Innovations

A Centre of Excellence within the University of Oxford to explore new models for how to do pharmaceutical and other medical Research and Development better, faster and cheaper, and so accelerate the availability of effective, safe and affordable therapies to patients.

## ISPOR Educational Symposium *Personalised Medicine*



**Robert S. Epstein, MD, MS**  
President  
United BioSource Corporation (UBC)

November 8, 2011

## It's all about change

*"We live in a moment of history where change is so speeded up – that we begin to see the present only when it is already disappearing."*

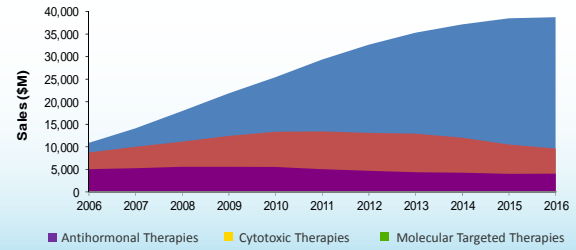
R.D. Laing  
Scottish psychiatrist - writer



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## The present is already about personalised medicines in oncology

In 2006, the molecular targeted therapies overtook the cytotoxic therapies for the first time, with sales of \$10.7 billion and \$8.9 billion, respectively



Source: Datamonitor forecasts and MIDAS Sales Data, IMS Health, April 2007.



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## Newer cancer drugs that target pathways that are personalised

Drug	Pathway	Condition	Test
Gleevec® Sprycel® , Tasigna®	BCR-ABL kinase	Chronic Myelogenous Leukemia	BCR-ABL copies
Herceptin®	HER-2 receptor	Breast cancer	HER-2 status
Rituxan®	CD-20 protein	Lymphoma	FCGR3A gene
Avastin®	VEGF	Colon cancer	VEGFA?
Xalkori®	ALK4	Lung cancer	ALK4
Tarceva® , Iressa®	EGFR kinase	Lung, pancreatic cancer	EGFR
Sutent®	Tyrosine kinases	GI cancer	KIT mutations
Erbbitux® , Vectibix®	EGFR	Colon, head/neck cancer	KRAS mutations



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## Anticancer Drugs Approved by the Food and Drug Administration (FDA) with Labeling Regarding Pharmacogenomic Biomarkers\*

### Type of Biomarker and Associated Drug

Biomarker – pharmacokinetic effect	Biomarker – pharmacodynamic effect	
<b>TPMT</b> Mercaptopurine Thioguanine	<b>EGFR</b> Cetuximab Erlotinib Gefitinib Panitumumab	<b>ABL</b> Imatinib Dasatinib Nilotinib
<b>UGT1A1</b> Irinotecan Nilotinib	<b>KRAS</b> Cetuximab Panitumumab	<b>C-Kit (KIT)</b> Imatinib <b>HER2/neu (ERBB2)</b> Lapatinib Trastuzumab
		<b>Estrogen receptor</b> Tamoxifen

\* Data are from FDA's pharmacogenetics web site ([www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm](http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm)). The biomarkers have been separated into pharmacokinetic effect (drug metabolism) and pharmacodynamic effect (drug target). Biomarkers for cytogenetic alterations have been excluded.

Source: Wang L et al. N Engl J Med 2011;364:1144-1153.



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## What is personalised medicine?

Using medicines (selecting drug, dose, duration of therapy) based on the genetics of the individual patient

Personalising therapy according to patient characteristics



## Diagnostics – how are they viewed?

### ■ Prediction of drug response or toxicity

- > Hepatitis C (gene type of the virus)
- > HIV/AIDS (HLA B\*5701)

### ■ Monitoring for drug response

- > Leukemia (BCR-ABL)
- > Circulating tumor cells (characterization)

### ■ Prognosis

- > Breast cancer



## Putting payer perspective in perspective

### ■ Statistical Significance

- > Multiple comparisons
- > Interim looks
- > Type I/II errors

### ■ Clinical Significance

- > How much change matters?
- > Is the improvement clinically meaningful?



## Putting payer perspective in perspective

### ■ Statistical Significance

- > Multiple comparisons
- > Interim looks
- > Type I/II errors

### ■ Clinical Significance

- > How much change matters?
- > Is the improvement clinically meaningful?

### ■ Payer Significance

- > Will the PM approach change clinical practice and outcomes compared with usual care?



## Top 5 Issues for Payers in PM

- Clinical Utility
- Unmet need
- Practical considerations
- Unintended consequences
- Test characteristics

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## Clinical Utility

- "Clinical utility" is a term that is widely used in medicine to describe the relevance and usefulness of an intervention in patient care.
- Despite general agreement that clinical utility assessments are multidimensional and may include economic, clinical, and/or humanistic domains, **there is no consensus on its definition** or how to robustly demonstrate it to the satisfaction of multiple stakeholders.

Source: Lesko LJ, Zineh I, Huang SM. What is clinical utility and why should we care? 2010; CPT:88(6):729-723.

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## PREDICT-1 demonstrated evidence of clinical utility

- RCT ~1600 patients in 19 countries
- ~ 800 received test first, other ~ 800 did not
- If positive (5.6%) – screened out
- Compared 'usual care' with pre-screened group for incidence of immunologically confirmed hypersensitivity reaction

Source: Mallal S, Phillips E et al. HLA-B\*5701 screening for hypersensitivity to Abacavir. NEJM 2008;358:568-579.

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## PREDICT-1 Results

- **0% of the pre-screened group experienced immunologically confirmed hypersensitivity in follow-up (0/802)**
- **2.7% of the non-screened group had immunologically confirmed hypersensitivity (23/842)**

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## Payer impressions

- Didn't like that the evaluation was conducted in tightly controlled environment – i.e., will practitioners act on the results in Real World?
- Mainly a caucasian population – generalizable?
- Some clinical events occurred in the pre-screened group – but weren't patch test positive – why?
- **NET NET** – *Great internal validity, less so on external validity*

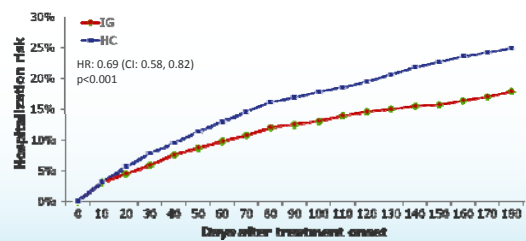


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## Results from MM-WES – all cause hospitalizations Intention-to-treat analyses\*

### All cause



\*Adjusted for age, comorbid conditions, drugs, propensity score, indications, prior GI bleed or VTE, history of prior hospitalization

Source: Epstein RS, Moyer TM et al. Warfarin genotyping reduces hospitalization rates from the MM-WES (Medco-Mayo Warfarin Effectiveness Study). JACC:2010;55(25):2804-2812.



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## Payer impressions

- Non-randomization – despite matching and statistical control using propensity matching – was not conclusive for all payers
- Event rates were higher than anticipated (though we subsequently validated in 55 plans with similar rates)
- **NET NET** – *great external validity, less great internal validity*



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## NICE quote on evidence

“Experiment, observation and mathematics, individually and collectively, have a crucial role in providing the evidentiary basis for modern therapeutics. **Arguments about the relative importance of each are an unnecessary distraction.** Hierarchies of evidence should be replaced by accepting – indeed embracing – a diversity of approaches.”

Sir Michael Rawlins, NICE, Lancet 2008



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## Comparative/Relative Effectiveness – New Kid on Block for Generating Evidence?

### Pierre Louis (1787-1872): Father of CER?

- "what was to be done in order to know whether bloodletting had any favorable influence on pneumonitis? ...to ascertain whether other things being equal, the patients who were bled on the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, or 4<sup>th</sup> day recovered more readily than those bled at a later period...it was necessary to estimate the influence of age or any other circumstance on the appreciable effects of bloodletting



Morabia. J Clin Epi 1996



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## But – here we are in 2000s.....

- Leeches inject hirudin that inhibits platelet aggregation and the coagulation cascade
- This relieves venous congestion
- Clinical studies in the 2000s showed 70-80% success rate in salvaging tissue (skin grafts, reattachment surgery)
- Leeches gained 510K FDA clearance in 2004 – Recarimpex SAS was the company involved.



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## And a National Payer (Aetna) covers leeches

- Clinical Policy Bulletin:  
Bio-Surgery: Medicinal Leech Therapy and Medical Maggots
- Number: 0556

Aetna considers medicinal leech (*Hirudo medicinalis*) therapy *medically necessary* for any of the following conditions:

- > Poor venous drainage (venous congestion/venous outflow obstruction); or
- > Salvage of vascularly compromised flaps (muscle, skin, and fat tissue surgically removed from one part of body to another); or
- > Salvage of vascularly compromised replants (limbs or other body parts re-attached after traumatic amputation).



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## Actual Origin of CER may be...



- Also may be the origin of the expression –
- Blowing smoke up one's a\*\*



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## Concluding Thoughts



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## All of us can make a difference

"If you think you're too small to have an impact, try going to bed with a mosquito in the room."

*Dame Anita Roddick, 1942-2007,  
British businesswoman, humanitarian,  
founder of The Body Shop*

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## The Economics of Personalised Medicine

Research

Consulting

Professor Adrian Towse

Office of Health Economics  
ISPOR Madrid

8<sup>th</sup> November, 2011



## Practical Issues and Obstacles to the Use of PGx in Health Care Systems

- Development of the Science
- Establishing the strength of the evidence base
  - The clinical utility challenge
- The Regulatory Regime
  - The regulatory challenge
- Need for Appropriate Pricing and Reimbursement
  - The reimbursement challenge
  - The IP challenge



**UNIVERSITY of WASHINGTON**

## Human Genome Project—10 Years On

**The New York Times**

**A Decade Later, Genetic Map Yields Few New Cures**  
 By NICHOLAS WATSE

Two years after President Bill Clinton announced that the first draft of the human genome was complete, medicine has yet to see any large part of the promised benefits.

For biologists, the genome has yielded one insightful surprise after another. But the primary goal of the \$3 billion Human Genome Project — to ferret out the genetic roots of common diseases like cancer and Alzheimer's and then generate treatments — remains largely elusive. Indeed, after 10 years of effort, geneticists are almost back to square one in knowing where to look for the roots of common disease.

**• Disappointment or New Foundation?**



**Revolution Postponed: Why the Human Genome Project Has Been Disappointing**

The Human Genome Project has failed so far to produce the medical miracles that scientists promised. Discoveries are now shrouded over what, if anything, went wrong—and what needs to happen next.

By Howard S. Wald / October 16, 2001 11:24


© 2001 The New York Times Company

A decade ago biologists and medical scientists alike gushed with optimism about the medical promise of the \$3-billion Human Genome Project. In announcing the first rough draft of the human "book of life" at a White House ceremony in the summer of 2000, President Bill Clinton predicted that the genome project would "revolutionize the diagnosis, prevention and treatment of most, if not all, human diseases."


### The clinical utility challenge

- It makes sense to have new therapies targeted at the patient groups who benefit most
- Evidence of clinical utility as a precursor of establishing value needs to be present
- Drug-PGx co-development offers the prospect of well designed studies allowing for the demonstration of clinical utility and development of economic evidence
- Payers and public research bodies can also sponsor studies – both RCT and observational
- Less clear the diagnostics industry can do so



### The clinical utility challenge: pharmaceutical company sponsorship


- **EGFR biomarkers** Two phase III clinical trials have provided evidence to support the use of EGFR mutational testing to select advanced NSCLC patients for first line treatment with EGFR-TKIs.
- **The link between HSR to abacavir** and the presence of the HLA-B\*5701 allele was established by GSK through a large retrospective study.
- **KRAS mutation:** Although the test is a predictive companion diagnostic, it was developed after the drugs were launched. A strong association with KRAS was discovered in an ex post sub group analysis.
- **HER 2:** The first test for HER2/neu over expression was developed as a companion diagnostic.
- **BCR-ABL testing and imatinib in CML:** Clinical utility was demonstrated by the results of the IRIS clinical trial study.



04/11/2010 17

### The clinical utility challenge: Oncotype DX®

- Oncotype DX® predictive power was clinically validated using tissue samples from a clinical trial. A prospective clinical trial (TAILORx) sponsored by the US NCI, is currently underway to evaluate Oncotype DX®.
- United Health, has entered into a risk-sharing agreement with Genomic Health, the suppliers of the Oncotype Dx® test. Payment depends on the extent to which clinical decision making changes.



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### The regulatory challenge

- Two issues:
  - Whether the evidence hurdle needs to be raised for some diagnostic tests?
  - How companion diagnostics are to be treated in the regulatory process and the implications for drug development and licensing?



### The reimbursement challenge

- In our examples the studies that demonstrate clinical utility are funded by drug manufacturers, payers, or publicly funded biomedical research institutes.
- Reimbursement prices do not appear to encourage diagnostic manufacturers to invest in evidence collection via large studies (RCT or observational).
- More needs to be done to align prices with evidence of value.



### The IP challenge

- Diagnostic test developers also need to be able to protect their intellectual property
- One way of doing this, linked into improved regulation and to improved evidence generation, could be to provide some form of “data exclusivity” for evidence generated by a company to support clinical utility



### ISPOR PGx SIG

- **Submitted paper to Value in Health fall 2011 entitled:**
- Challenges in the Development and Reimbursement of Personalized Medicine: Payer and Manufacturer Perspectives and Implications for Health Economics and Outcomes Research:
  - key development and reimbursement considerations from the payer and manufacturer perspectives.
  - five key areas identified in which health economics and outcomes research (HEOR) best practices could be developed to improve value assessment, reimbursement, and patient access decisions for personalized medicine.
  - key gaps in HEOR best practices, decision standards, and value assessment processes are also discussed, along with next steps for evolving HEOR practices in the expanding field of personalized medicine.



## ISPOR PGx SIG presentations

- Faulkner E, Anemans L, Holtorf A-P, Longacre M. Value-based reimbursement for personalized medicine: where do we stand?. International Society for Pharmacoeconomics and Outcomes Research, 13th Annual European Congress, Madrid, Spain. November 2011. THIS SESSION IS ON TUES ISSUE PANEL TRACK AT 10-11 – may be good to note for attendees
- Faulkner E, Quinn B, Trakas K, Garrison L. What can we learn from successes and failures in personalized medicine. Implications for evolving health outcomes and economics research practices. International Society for Pharmacoeconomics and Outcomes Research, 16th Annual International Meeting, Baltimore, MD, May 2011.
- Faulkner E, Towse A, Ossa D, Siebert. Are diagnostics and personalized medicine in flux? Implications of global policy changes for health economics and outcomes research. International Society for Pharmacoeconomics and Outcomes Research, 13th Annual European Congress, Prague, Czech Republic. October 2010.
- Faulkner E, Malone D, Austin F, Watkins J, Veenstra D. Issues and challenges in the development and reimbursement of personalized medicine: How can health economics and outcomes research help? International Society for Pharmacoeconomics and Outcomes Research. ISPOR 14th Annual International Meeting, Orlando, FL, May 2010.
- Faulkner E, Lieven Anemans, Katherine Payne, Uwe Siebert. The devil is in the details: international comparison of technology assessment processes and payer uptake of personalized medicine and implications for the field. International Society for Pharmacoeconomics and Outcomes Research, 12<sup>th</sup> Annual European Congress, Paris, France. October 2009.
- Faulkner E, Patricia Deverka, Penny Mohr, and David Veenstra. Developing and addressing payer evidence requirements for molecular diagnostics and personalized medicine: how can health outcomes and economics approaches help fill the gap? International Society for Pharmacoeconomics and Outcomes Research, Orlando, FL, May 2009.

