Will availability of drugs become an issue? The physicians and payers perspective  

*Paul Cornes*

2\textsuperscript{nd} July, 2016

Dr Paul Cornes  

European School of Oncology - Working Party on Access to Innovation & Comparative Outcomes Group, Bristol, UK
Dr Paul Cornes
Disclosures June 2016

- Salary received:
  - United Kingdom National Health Service

- Honoraria received:
  - Accord Healthcare
  - Amgen
  - Bernstein
  - British Medical Journal
  - European Generics Association
  - Global Academy of Health Sciences
  - Hospira
  - Janssen
  - Lilly
  - Merck Serono
  - Napp
  - National Cancer Society Malaysia
  - Pharmaceutical Association of Malaysia
  - Pfizer
  - Roche
  - Sandoz
  - Teva

These slides and their content were created by Dr Paul Cornes.

Please let me know if there are errors or omissions.
Session XVIII: Keynote Lecture:
Health Economics and Cost,

July 2nd, 2016

Will availability of drugs become an issue?
The physicians and payers perspective

Dr Paul CORNES, Bristol, UK
paul.cornes@yahoo.co.uk
I value my work with international colleagues.
We cooperate or we fail

cancer has the most devastating economic impact of any cause of death in the world.

Cancer causes the highest economic loss of all of the 15 leading causes of death worldwide.

WHO: Cancer world's top killer since 2010

17 percent of all 'healthy' years lost in the European Union

The total economic impact of premature death and disability from cancer worldwide is $2.5 trillion.

170 million years of “healthy life” lost due to death and disability from cancer in 2008

There is a cost to cancer
There is a cost to cancer care

Be positive - “Think about health spending as not consumption but investment”

Spending is not a negative – it is a positive good

We are treating the worlds most important disease – its greatest killer
Good news for medicine

- Basic cancer science is paying back on its investment
- One medical paper a minute is added to the PubMed US National Library of Medicine

*Be positive - “Think about health spending as not consumption but investment”*
Good news for cancer treatment: worldwide – more people survive cancer

- Reduction in cancer deaths –

Good news for cancer treatment: Cancer survival is improving

Median Survival of Cancer in the UK has risen from 1 to 10 years since 1971

1971, 50% 1 year survival
2010, 50% 10 year survival

Good news for cancer medicine:

Estimated - new medicines have accounted for 50-60 percent of the increase in cancer survival rates since 1975.
Good news for cancer treatment: Innovation in cancer drugs

At this rate our decade could add more than 100 new cancer drugs by 2020

- <1960: 5 cancer drugs
- 1960s: + 2 more
- 1970s: + 18 more
- 1980s: + 14 more
- 1990s: + 24 more
- 2000s: + 23 more
- 2010-15: + 43 more in only 5 years

Good news for cancer treatment: Innovation in cancer drugs

- Medicines in development in 2015

Almost two-thousand cancer medicines are in development at any one time

New targeted precision medicines are transforming cancer care

Chemotherapy era vs. targeted medicines era

Examples where survival has more than tripled

We want these medicines for our patients

The possibility at the millennium, 2000

The complexity of 200 different cancers may be explained by a few unregulated pathways.

And so the diversity of cancer might be treated by a limited panel of concurrent targeted precision therapies.

Where were we?

I am sorry to report that you have breast cancer

Tell me doctor – what have I got?

Anatomic diagnosis

- Malignant Neoplasm of Female Breast
- ICD-10-CM (Category C50)
- Nipple and areola – right, left, unspecified
- Central portion – right, left, unspecified
- Upper-inner quadrant – right, left, unspecified
- Lower-inner quadrant – right, left, unspecified
- Upper-outer quadrant – right, left, unspecified
- Lower-outer quadrant – right, left, unspecified
- Axillary tail – right, left, unspecified
- Overlapping not stated – right, left, unspecified
- Unspecified location – right, left, unspecified

I am sorry to report that you have breast cancer type

Tell me doctor – what have I got?

Breast cancer is now thought of as at least ten separate diseases, each with a different cause, life expectancy and needing a different treatment [2]

Where are we heading?

The Cancer Genome Atlas is a working Map of functional and actionable alterations across different tumour types [4]

Describes pathways deregulated

And drug class required to counter it

Where are we heading?

2016: Targeting two deregulated pathways with lapatinib and trastuzumab - Tumours can be gone in as short as 11 days! [5]

Describes pathways deregulated

And drug class required to counter it

Tumours shrunk 'dramatically' in 11 days

By James Gallagher
Health editor, BBC News website

10 March 2016 | Health

A pair of drugs can dramatically shrink and eliminate some breast cancers in just 11 days, UK doctors have shown.

They said the "surprise" findings, reported at the European Breast Cancer Conference, could mean some women no longer need chemotherapy.

Where are we heading?

“Basket trials” now mean we will treat cancers by genomic diagnosis, not anatomic site [4]

Basket Trials and the Evolution of Clinical Trial Design in an Era of Genomic Medicine

Amanda J. Redig, Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA
Pasi A. Jänne, Dana-Farber Cancer Institute, Harvard Medical School, and Brigham and Women’s Hospital, Boston, MA
See accompanying article doi: 10.1200/JCO.2014.59.8433

Since the days of the ancient Greeks, the pathologic hallmarks of malignancy have been reflected in the language of oncology. Hippocrates was the first to use carcinoma—or crab—to describe the familiar irregular mass of tumors. Some emesis trials now mean we will treat cancers by genomic diagnosis, not anatomic site [4].
Where are we heading?

With 3 key steps deregulated – we need 3 concurrent cancer therapies

How should we treat it?

Where are we heading?

With 3 key steps deregulated – we need 3 concurrent cancer therapies

How should we treat it?

Where are we heading?

With 3 key steps deregulated – we need 3 concurrent cancer therapies

How should we treat it?

Where are we heading?

With 3 key steps deregulated – we need 3 concurrent cancer therapies

The average cost per month for a branded oncology drug in the U.S. is now approximately $10,000 [2]

$10,000 \times 3 \times 12 = $360,000 per year

Will my health insurance cover that?
So - We Have a Problem …

CAN WE AFFORD THE WAR ON CANCER?

Immunotherapy vaccines could extend survival in a handful of cancers. But personalizing treatment, payers argue, is not sustainable. Where should the line be drawn?

BY ED SILVERMAN

Two years ago, the U.S. Food and Drug Administration took a step that some thought would never occur — it approved the sipuleucel-T (Provenge) vaccine for late-stage prostate cancer. The move came after a protracted episode involving allegations of conflicts of interest among a pair of FDA advisory committee members who reviewed the tending a life by 4.1 months is worth the price of Provenge. It has also prompted larger questions about the underlying technology and the need to develop more vaccines.

Provenge is made by culturing a patient’s immune cells with a recombinant antigen. The individualized product is then infused back into the patient, activating the immune system to target and attack the cancer. This “immunotherapy” underscores the move toward personalized

Economics is not primarily about saving money. It is about using scarce resources as efficiently as possible.

Economists never say “cheap” or “expensive” - they say “cost-effective” or “not cost effective”.

You know more economics than you think.
You know more economics than you think

Economics or Οἰκονομία – is a Greek word

Oikos = “the household”
+ Nomos = “wise rules”

Economics - “wise rules for managing the household”

“Health economics” = Wise rules for managing the hospital
The 2 “E”s of pharmacology: efficacy, effectiveness,

<table>
<thead>
<tr>
<th>Can it work?</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Does it work in reality?</td>
<td>Effectiveness</td>
</tr>
</tbody>
</table>
The 3 “E”s of pharmaco-economics: efficacy, effectiveness, efficiency

<table>
<thead>
<tr>
<th>Can it work?</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Does it work in reality?</td>
<td>Effectiveness</td>
</tr>
<tr>
<td>Is it worth doing compared to other</td>
<td>Cost-effectiveness</td>
</tr>
<tr>
<td>things we could do with the same</td>
<td>= Efficiency</td>
</tr>
<tr>
<td>money?</td>
<td></td>
</tr>
</tbody>
</table>
Is it worth doing compared to other things we could do with the same money?

A Euro can only be spent once

Once money has been spent on one thing – it is a lost “opportunity” to spend it on something else

economists call this the “opportunity cost” of spending
Focus care to where it helps us live longer and live better

Peter Orszag, director of the White House Office of Management and Budget, May 2009 interview with NPR.

“Estimates suggest that as much as $700 billion a year in health care costs do not improve health outcomes. They occur because we pay for more care rather than better care”

The power of health economic thinking

- Assuming we worry about costs, and that some public funded health care is essential: could we perform better?

- 185 publicly-funded interventions in the United States cost about $21.4 billion per year, for an estimated saving of 592,000 years of life (considering only premature deaths prevented).

- Re-allocating those funds to the most cost-effective interventions could save an additional 638,000 life years if all potential beneficiaries were reached.

Tengs TO. Dying too soon: how cost-effectiveness analysis can save lives. Irvine, California, University of California, National Center for Policy Analysis, 1997 (Policy Report No. 204)
Payers are predicting that our treatment model for cancer is unaffordable

- Without a focus on value - the costs of cancer will rise dramatically.
- Available projections from the US [1] United Kingdom (UK) [2] and Australia [3] suggest that if cancer costs increase at current Compound Annual Growth Rates of 3.6-5.2% (CAGR)
  - dramatic budget increases will be needed by 2025

There is no new money to fund a wave of investment in innovative medicine

- Since 2008 there has been a massive gap between the value of what is earned and what is being spent.

Ref: [1] Matthew Lynn. All the signs point to a new recession – a worse one. The Spectator, 5 March 2016. http://www.spectator.co.uk/2016/03/the-next-recession/

We Have a Problem: More Cancer to Treat

Figure 2.1a: Average, Annual Cancer Incidence Rates by Age Category, 1992-1996 (Linear Scale)

Relationship of cancer incidence with age

Peak age for cancer is 70-84 years

The average life expectancy in 2009 was 67

Planning for the Future: What Will Happen to Costs?

What is the driver for increased spending: Aging populations or medical treatment?

But we may not be able to afford innovation in Medical treatment

We can afford to age

We have a problem: Treatment costs are rising

Monthly cost of new cancer drugs by year of approval

Cancer drug costs rise 5x faster than other classes of medicine

Our failure to control costs is not new:

Monthly and Median Costs of Cancer Drugs at the Time of FDA Approval
1965 - 2014

Median costs of a new cancer drug $100,000 USD per patient per month in 2035

The problem has been consistent since the 1970s

Costs are rising exponentially

Log Cost

Ref: [1] Bach P. Limits on Medicare’s ability to control rising spending on cancer drugs. NEJM. 2009 Feb 7
When will new cancer drug costs fall?


Median costs of a new cancer drug $100,000 USD per patient per month in 2035

Costs are rising exponentially

All the advances in the understanding of cancer biology and new technology have failed to reduce the rising price of commercial drug development.
Does it always have to get more expensive?

MOORE’s Law

Does it always have to get more expensive?

MOORE’s Law
EROOM’s Law

Does it always have to get more expensive?

MOORE’s Law

ERROOM’s Law

"We are at a crossroads for affordable cancer care, where our choices—or refusal to make choices—will affect the lives of millions of people."

The Payers’ perspective: Medical strategies will have to change

- **Pre-EBM - Evidence Based Medicine**
  - Focus on a novel mechanism of action? *Response = CR, PR, SD, PD*

- **EBM - Evidence Based Medicine**
  - Focus on efficacy *OS, QoL*

- **VBM - Value Based Medicine**
  - Focus on effectiveness and “value” to stakeholders *Cost/QALY*

---

**EBM “Does this intervention make you live significantly longer or live better?”**

**VBM “Is this worth doing compared with other things we could do with the same resource?”**
Can payers trust physicians to lead on value and cost control?

- Physicians want to give the best health chances to each patient
- Payers want to buy the most health from the limited resources

Can payers trust physicians to lead on value and cost control?

- Physicians want to give the best health chances to each patient
- Payers want to buy the most health from the limited resources

Principles - ESMO Scale for Assessing Value of Cancer Drugs

1. Cure takes precedence over deferral of death.
2. Direct endpoints, such as overall survival and quality of life, take precedence over surrogates such as progression-free survival (PFS) and response rate (RR).
3. Disease-free survival in curative disease is a more valid surrogate than PFS and RR in noncurative disease.
4. Cost is not taken into account

Guidelines that include cost without value may offer no better help - NCCN

Guidelines that include cost without value may offer no better help - NCCN

NCCN Panel members score each measure using a standardized scale from “1” to “5” with “1” being the least and “5” the most favorable.

[A] Affordability refers to the overall cost of an intervention including drug cost, required supportive care, infusions, toxicity monitoring, management of toxicity, probability of care being delivered in the hospital, etc. with less expensive interventions being rated more highly than more expensive ones. The scale used to measure affordability is:

5 Very inexpensive
4 Inexpensive
3 Moderately expensive
2 Expensive
1 Very expensive
Guidelines that include cost without value may offer no better help - NCCN

NCCN Panel members score each measure using a standardized scale from “1” to “5” with “1” being the least and “5” the most favorable.

Cost-effectiveness is not shown

But no actual costs are given!

[A] Affordability refers to the overall cost of an intervention including drug cost, required supportive care, infusions, toxicity monitoring, management of adverse effects, probability of care being delivered in the hospital, etc. with less expensive interventions being ranked more highly than more expensive ones. The scale used to measure affordability is:

5 Very inexpensive
4 Inexpensive
3 Moderately expensive
2 Expensive
1 Very expensive

a high cost regimen may be highly effective – and so good value

Can payers trust physicians to lead on value and cost control?

- Payers ask oncologists - have we advocated for more care or better care?

**Early Trends Among Seven Recommendations From the Choosing Wisely Campaign**

Alan Rosenberg, MD¹; Abiy Agiro, PhD²; Marc Gottlieb, MPA¹; John Barron, PharmD²; Peter Brady, MBA¹; Ying Liu, MS¹; Cindy Li, MSc¹; Andrea DeVries, PhD²

[+] Author Affiliations


- 2 of 7 ineffective interventions – marginal decrease
- 5 of 7 ineffective interventions – increased

The options for future health spending include the following:

1. Carry on spending at current rates – postpone the inevitable decision to contain spending

   Untenable in the medium term

2. Carry on spending at current rates and improve efficiency and productivity
   • that is, buy extra time before confronting the inevitable decision to contain spending

   Viable in the medium term

3. Align health spending growth to general, long-term growth in the economy as a whole
   • with possible adjustments to devote a modestly greater share of GDP to health care as GDP grows.

Only long term viable option if comprehensive Health care is to remain affordable

The options for future health spending include the following:

1. Carry on spending at current rates – postpone the inevitable decision to contain spending.

2. Carry on spending at current rates and improve efficiency and productivity – that is, buy extra time before confronting the inevitable decision to contain spending.

3. Align health spending growth to general, long-term growth in the economy as a whole – with possible adjustments to devote a modestly greater share of GDP to health care as GDP grows.

What strategy should we advocate in the next generation ESMO guidelines?

Untenable in the medium term

Viable in the medium term

Only long term viable option if comprehensive Health care is to remain affordable

Leadership on value: requires that we understand the payer’s perspective

- **Important Similarities Between Physicians and Economists**
  1. Realistic approach to life’s problems
  2. Reliance on quantitative information
  3. Often must make difficult choices in the face of uncertainty
  4. Good decisions require comparing benefits and risks (costs)
Leadership on value: requires that we understand the payer’s perspective

- **Big Difference Between Physicians and Economists**

1. Physicians are usually concerned with an individual patient or small numbers of patients
2. Economists are usually concerned with large aggregations:
   - organizations, industries, governments,
   - society as a whole

- This explains the tension between payers and physicians over medicines optimization and drug cost control

Payers for health services want the to buy the most health benefit for the greatest number of patients

Physicians want the best care for each patient
Leadership on value:

- We must help to find the investment for continued innovation

It can be hard to determine the true value of innovation in just the short term
Leadership on value: Personalised precision targeted therapy is still in development

MOORE’s Law
EROOM’s Law

It can be hard to determine the true value of innovation in just the short term

Leadership on value: Personalised precision targeted therapy is still in development

It can be hard to determine the true value of innovation in just the short term

Leadership on value: Personalised precision targeted therapy is still in development

Repeat biopsies may be obsolete to direct therapy over time

UC Davis, USA
Sequenced blood & Tumour from 15,000 patients with 98% accuracy in finding target gene markers

It can be hard to determine the true value of innovation in just the short term

## Waiting for data on value? Example – Trastuzumab

<table>
<thead>
<tr>
<th>Year</th>
<th>Outcome data</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1999</td>
<td>In 25% of advanced breast cancer that over-express the HER biomarker, it makes 21% of tumours respond</td>
<td>1</td>
</tr>
<tr>
<td>2001</td>
<td>It adds 5 months of extra life in HER+ advanced breast cancer</td>
<td>2</td>
</tr>
<tr>
<td>2005</td>
<td>As adjuvant therapy, increased Overall Survival 4.8% absolute</td>
<td>3</td>
</tr>
<tr>
<td>2005</td>
<td>As adjuvant therapy, 1 year trastuzumab is as good as 2y for preventing relapse</td>
<td>4</td>
</tr>
<tr>
<td>2011</td>
<td>Adjuvant therapy trials durable 4-5% absolute benefit long term</td>
<td>5</td>
</tr>
<tr>
<td>2015</td>
<td>After 8.3 years from Adjuvant therapy - OS advantage is now 7.5% absolute</td>
<td>6</td>
</tr>
<tr>
<td>2015</td>
<td>Combined with Pertuzumab – it adds 15 months of life in HER+ advanced breast cancer</td>
<td>7</td>
</tr>
</tbody>
</table>


The value of Trastuzumab became progressively clearer over time.
Waiting for data?
Example – Trastuzumab in the UK

The use of trastuzumab – in the first 10 years since launch (expressed in mg/case of breast cancer) [2]


Similar effect seen in all EU nations

The value of Trastuzumab became progressively clearer over time [1]
Waiting for data?

Example – Trastuzumab in the UK

Over 10 years since approval, UK uncertainty over value denied many women what we now know to be a cost-effective 7.5% durable survival advantage [3]

The use of trastuzumab – in the first 10 years since launch (expressed in mg/case of breast cancer) [2]

More UK women missed out on cures from trastuzumab

Than gained

Similar effect seen in all EU nations

The value of trastuzumab became progressively clearer over time [1]
Waiting for data on value? Example – Imatinib in the 13 wealthiest EU nations

The value of Imatinib became progressively clearer over time

The use of imatinib in the first 8 years since approval (expressed as mg/case of leukaemia)

Waiting for data on value? Example – Imatinib in the 13 wealthiest EU nations

The lost health value is real – with imatinib, Chronic Myeloid Leukaemia patients return to a normal life expectancy [2]

Less than 2/3 of patients gained access

The use of imatinib in the first 8 years since approval (expressed as mg/case of leukaemia)

Falling costs of sequencing offers a new level of precision targeting of therapies

- The UK NHS:
- Aims to sequence tumour and patient DNA from 70,000 cases

Personalised therapy will get more precise – and more cost effective

- Evolution in the use of biomarkers

By excluding those unlikely to benefit from a targeted therapy

The rate of non-responders should fall

And both clinical effectiveness & cost-effectiveness should rise

Leadership on value:

- We must help to find the investment for continued innovation
- There is money within our budgets we could release to reinvest
We must recognise: the potential of a treatment is not the same for all patients

- Have our guidelines promoted treatments of marginal benefit?

![Graph showing the potential of treatment to benefit a patient vs. the magnitude of effect. The graph categorizes treatments into High, Moderate, Marginal Inappropriate, and Futile based on their potential to benefit a patient and the magnitude of harm. Examples include Chemotherapy at the end of life and PSA tests in asymptomatic men with life-limiting comorbidity.]
Physicians are surprisingly good at identifying marginal or inappropriate care

- Studies conducted in the UK [1,2] Norway [3] and Brazil [4] have all found that healthcare professionals are less likely to choose aggressive courses of treatment than patients.

- Indeed when the healthcare professionals themselves have cancer they are less likely to pursue the ‘futile care’ they have observed over the course of their career [5]
Have we been making appropriate claims for expensive marginal therapies?

Abstracts have become increasingly optimistic over time - a relative increase of 880% in the use of these words.

Have we been making appropriate claims for expensive marginal therapies?

Abstracts have become increasingly optimistic over time - a relative increase of 880% in the use of these words.

Have we been making appropriate claims for expensive marginal therapies?

Abstracts have become increasingly optimistic over time - a relative increase of 880% in the use of these words.

Have we been making appropriate claims for expensive marginal therapies?

Abstracts have become increasingly optimistic over time - a relative increase of 880% in the use of these words.

Leadership on value:

- Should the ESMO minimum criteria be applied to existing therapies and patient groups?

What strategy should we advocate in the next generation ESMO guidelines?
"All countries can do something, many of them a great deal, to improve the efficiency of their health systems, thereby releasing resources that could be used to cover more people, more services and/or more of the costs."

Ten leading causes of inefficiency:

1. Medicines: underuse of generics and higher than necessary prices for medicines

- Lack of alternative care arrangements; insufficient incentives to discharge; limited knowledge of best practice.
- Insufficient knowledge of clinical-care standards and protocols; lack of guidelines; inadequate supervision.
- Unclear resource allocation guidance; lack of transparency; poor accountability and governance mechanisms; low salaries.
- Funding high-cost, low-effect interventions when low-cost, high-impact options are unfunded. Inappropriate balance between levels of care, and/or between prevention, promotion and treatment.
Saving from within the current budget: Generics

Generic Market Shares in Europe 2006

- % Share (value)
- % Share (volume)

In 2006 only 4 EU countries achieved 2/3 or more generic prescriptions [1]

Saving from within the current budget: Biosimilars

- Biosimilars of just 2 drugs reimbursed by the NHS –
- Could save NHS England 3.4% of its total Hospital drugs budget

Biosimilars - show great variation in uptake from <1% to 100%

What are Biosimilar medicines?

- These are copies of patient expired biologic medicines approved by a comparative “Biosimilar” regulatory pathway.

- They have the same indications, quality, safety and efficacy of the original reference medicine.

- They share the same International Drug Name (“INN”).

- They have been in use in Europe for a decade with no evidence that they perform any differently than the original reference drugs.

The only meaningful difference? - They cost less than the reference drugs that they copy.

Potential savings impact of biosimilars

- The cumulative potential savings to health systems in the five major European Union (EU) markets and the U.S., as a result of the use of biosimilars,
  - could exceed EUR50 billion in aggregate over the next five years and reach as much as EUR100 Bn

We are given clear leadership on Rational Medicine Use

"Medicine use is rational (appropriate, proper, correct) when
- patients receive the appropriate medicines,
- in doses that meet their own individual requirements,
- for an adequate period of time, and
- at the lowest cost both to them and the community."

Irrational (inappropriate, improper, incorrect) use of medicines
- is when one or more of these conditions are not met.”

Leadership on value:

- Should the ESMO minimum criteria be applied to existing therapies and patient groups?
- Should the next ESMO guidelines endorse a policy of generic substitution and early adoption of biosimilars?
- What strategy should we advocate in the next generation ESMO guidelines?
- Have we missed inexpensive innovation that we should be promoting first?
Question

Would you recommend your partner have adjuvant chemotherapy for resected stage III colon cancer with

1. 5FU+FA regimen

2. 5FU+FA+Oxaliplatin regimen

3. Another drug class

USA NCI – “FOLFOX has become the reference standard for…patients with stage III colon cancer”

OS benefit vs No Chemo = HR 0.78
12% absolute benefit

OS benefit vs No Chemo = HR 0.65
Additional 4.2% benefit

Cochrane review, 5 x RCTs; Overall Survival benefit HR 0.53

Treatment Option: H2 antagonists as adjuvant therapy for resected colorectal cancer

Cimetidine Cost = $2-4 per month of treatment [2]

Current Standard Adjuvant is Outpatient FOLFOX regimen - costs $34,000/6 months [3]

Question – take 2

- Would you recommend your partner have adjuvant chemotherapy for resected stage III colon cancer with

1. 5FU+FA regimen

2. 5FU+FA+Oxaliplatin regimen

3. Another drug class

Patients already take risks we find unacceptable in ESMO guidelines

Up to half of our patients already take unproven “alternative” therapies
Leadership on value:

What strategy should we advocate in the next generation ESMO guidelines?

- Should the ESMO minimum criteria be applied to existing therapies and patient groups?
- Should the next ESMO guidelines endorse a policy of generic substitution and early adoption of biosimilars?
- Should ESMO endorse the use of inexpensive unlicensed but not unproven therapies?
Should we advocate for unlicensed therapies?

**Aspirin As Secondary Prevention in Patients With Colorectal Cancer: An Unselected Population-Based Study**

Simer J. Bains, Milada Mahic, Tor Åge Myklebust, Milada Cvancarova Småstuen, Sheraz Yaqub, Liv Marit Dørum, Bjørn Atle Bjørnbeth, Bjørn Møller, Kristoffer Watten Brudvik and Kjetil Taskén

- In bowel cancer - Aspirin is associated with 9.4% absolute OS benefit
- And 11.5% absolute Cancer Survival
  - Study with >23,000 patients

**Effect of daily aspirin on risk of cancer metastasis: a study of incident cancers during randomised controlled trials**

Prof Peter M Rothwell, FMedSci, Michelle Wilson, Msc, Jacqueline F Price, MD, Prof Jill FF Belch, MD, Prof Tom W Meade, FRS, Ziyah Mehta, PhD

Published Online: 21 March 2012

DOI: http://dx.doi.org/10.1016/SC146-6736(12)20209-8

Glasgow UK has shown - Aspirin cuts off the inflammatory drive to metastasis that follows Colorectal surgery [2]

An effect confirmed repeatedly by meta-analysis of all Aspirin RCTs [3]
How cost effective can cancer therapy be:
10% OS benefit in GI cancer for <$1 a month?

Cost: 50 tablets for a dollar [4]

Glasgow UK has shown - Aspirin cuts off the inflammatory drive to metastasis that follows Colorectal surgery [2]

Ref confirmed repeatedly by meta-analysis of all Aspirin RCTs [3]
How cost effective can cancer therapy be:
10% OS benefit in GI cancer for <$1 a month?

Cost: 50 tablets for a dollar [4]

Risks increased bleeding in 0.8% of operations: NNH 125:1 [5]

Glasgow UK has shown - Aspirin cuts off the inflammatory drive to metastasis that follows Colorectal surgery [2]

The Repurposing Drugs in Oncology (ReDO) Project seeks to repurpose well-known and well-characterised non-cancer drugs for new uses in oncology.

- Screens old drugs for activity in cancer, and proposes
  - clinical trials – phase 2/3
  - Observational case by case studies

- First 6 studies

<table>
<thead>
<tr>
<th>Drug</th>
<th>Type</th>
<th>Existing Indication</th>
<th>Availability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mebendazole</td>
<td>Anthelminthic</td>
<td>Threadworm infections</td>
<td>Generic</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>Vasodilator</td>
<td>Angina</td>
<td>Generic</td>
</tr>
<tr>
<td>Cimetidine</td>
<td>H2-receptor antagonist</td>
<td>Peptic ulcer</td>
<td>Generic</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>Antibiotic</td>
<td>Respiratory tract infection</td>
<td>Generic</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>NSAID</td>
<td>Pain relief</td>
<td>Generic</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>Antifungal</td>
<td>Broad spectrum antifungal</td>
<td>Generic</td>
</tr>
</tbody>
</table>
Leadership on value:

What strategy should we advocate in the next generation ESMO guidelines?

- Should the ESMO minimum criteria be applied to existing therapies and patient groups?
- Should the next ESMO guidelines endorse a policy of generic substitution and early adoption of biosimilars?
- Should ESMO endorse the use of unlicensed but not unproven therapies?
- Should ESMO develop submission dossiers to license inexpensive therapies with the European Medicines Agency?
Should ESMO seriously consider becoming a drug developer?

Drug development is expensive: More than 278,800 Euros to gain approval for a single dose single indication medicine.

And a recurring E100,000 a year.

Should ESMO seriously consider becoming a drug developer?

Drug development is expensive:
More than 278,800 Euros to gain approval for a single dose single indication medicine
And a recurring €100,000 a year

June 1st 2016: EMA announces - Introduction of 100% fee reduction for products eligible to the PRIME scheme for micro, small or medium-sized enterprise and applicants from the academic sector

Time as treatment?

- **Question:** Would you recommend your partner have radical radiotherapy treatment for head & neck cancer....

1. In the morning 8-10am?
2. In the evening 4-6pm?
3. Whenever it’s convenient?
Time as treatment?

- 216 patients with head & Neck cancer randomised to morning (8-10 AM) vs. afternoon (4-6 PM) RT
  - stratified by radiation dose, smoking status, and centre

- Morning RT was associated with significantly less toxicity

Value isn’t just for drug treatment

- Intensity Modulated Radio-Therapy IMRT is the key “innovation” in radiotherapy
  - The Belgian Health Care Knowledge Centre found weak to moderate evidence it can reduce the toxicity of radiation therapy compared with conventional therapy [1]

- But it is more expensive [2]
  - US Government reimbursement is 3.3 to 5.5 times higher per treatment day
  - And planning treatment with IMRT costs 2.2 to 2.5 times more
  - The use of IMRT is rising [3]
  - along with costs [4]
Time as treatment? – Take 2

- Question: Would you now recommend your partner have radical radiotherapy treatment for head & neck cancer....

1. In the morning 8-10am?

2. In the evening 4-6pm?

3. Whenever it’s convenient?

Consider – if a drug, or IMRT reduced complications by 20-35% absolute – would you be advocating for it?

Rearranging patient RT bookings in your centre may be far more cost-effective than IMRT

But we cannot patent or bill for it!
Affordable Innovation: Views through the window as therapy: reduces hospital stays 8%

- 9 years records from one hospital [1]
  - Same window size each room on wards – but can look in different directions
  - No priority for assigning patients to any bed on a ward

- Patients with window views of trees spent less time in the hospital than those with views of brick walls:
  - 7.96 days vs 8.70 days per patient, P = 0.025
  - And use less painkillers, P < 0.01

Affordable Innovation: Views through the window as therapy: reduces hospital stays 8%

- Patients with window views of trees spent less time in the hospital than those with views of brick walls:
  - 7.96 days vs 8.70 days per patient, P = 0.025
  - And use less painkillers, P < 0.01

Affordable Innovation: Plants as therapy

- In a randomised trial –
  - Patients in hospital rooms with plants and flowers had significantly shorter hospitalizations, fewer intakes of analgesics, lower ratings of pain, anxiety, and fatigue, and more positive feelings and higher satisfaction

Ref: [1] Seong-Hyun Park et al. Therapeutic Influences of Plants in Hospital Rooms on Surgical Recovery. HortScience February 2009 vol. 44 no. 1 102-105
Affordable Innovation doesn’t just stop at cancer: Evening as a treatment?

- 2,012 hypertensive patients without diabetes
- Randomised to take blood pressure drugs morning or evening

The effect is consistent with all main types of drug:

- angiotensin receptor blockers (ARBs) (HR 0.39 [0.22, 0.69]; p < 0.001),
- ACE inhibitors (0.31 [0.12, 0.79], p = 0.015) and
- β-blockers (0.35 [0.14, 0.85], p = 0.021).

We cooperate or we fail

The most important thing we can do is learn from each other