Economic evaluations for cancer drug reimbursement policy-making in practice

My views from the Pharmacoeconomics Research Unit

JACLYN BECA, MSC
CCHE SEMINAR | JANUARY 2020
Outline

• Overview of cancer and the public cancer system
  – Cancer
  – Cancer drug funding
  – Ontario Health (Cancer Care Ontario)
  – Pharmacoeconomics Research unit: What we do and why we do it

• Pharmacoeconomics in cancer
  – Challenges in developing and interpreting economic evidence
  – Focus on modelling approaches: partitioned survival and Markov models
  – Future directions for the field
Overview of cancer and the public cancer system

• Cancer
Cancer

- What makes it important to study
- Some features that require special consideration
Cancer in Ontario

1 in 2 expected to be diagnosed

1 in 4 expected to die from cancer

Cancer is the leading cause of death in Ontario

Cancer incidence rate stable since 2001; mortality rate declining since 1983
Cancer

Cancer is the number 1 cause of death in Ontario [*]

- 39.7% ALL OTHER CAUSES
- 29.3% CANCER
- 19.4% CARDIOVASCULAR DISEASE
- 6.5% ACCIDENTS & SUICIDE
- 5.2% CEREBROVASCULAR DISEASES

https://www.cancercareontario.ca/en/cancerplan
Increased incidence and prevalence

NEW CANCER CASES ARE RISING[*]

MORE PEOPLE ARE SURVIVING AND LIVING WITH CANCER

As of 2013, the overall 5-year cancer survival rate was 65%, up from about 48% in the mid-1980s, though there was variation in survival across cancer types.[*]

585,016 people diagnosed with cancer in the past 30 years are still alive

Over half a million

https://www.cancercareontario.ca/en/cancerplan
Cancer is a word, not a sentence. A six-step, practical guide.

Dr Robert Buckman

Foreword by Dr Miriam Stoppard
Cancer

is

If you’re reading this book, you’re probably reeling.

Most people are knocked off balance and reeling when the diagnosis is a cancer. It’s the normal reaction: it’s what everybody experiences, and it’s

word.

The problem starts with the word cancer. There are so many overtones and associations attached, it is probably the most dreaded word in the English language. It brings with it, universally, queasy feelings of fear and doom. Many people describe the sensation as chilling, or as a sense of helplessness, or even as a foggy feeling of mental paralysis. They experience a

sentence.

A six-step, practical guide.

Dr Robert Buckman

Foreword by Dr Miriam Stoppard
Cancer is.

The whole problem starts with the fact that we are discussing a word, a single word that (as you’ll see) lumps together over two hundred different diseases. Yet that word should not be the end of a conversation, it should be a beginning – it should be the start of a fact-finding mission. As you will learn in the rest of this book, what really matters to you is not simply the diagnosis itself, but many other aspects of your situation that are much more important and relevant to you and your future.

Questions such as these:

- What specific disease – which of the two hundred different cancers – is it?
- What does it actually mean for your future?
- How does this particular cancer behave?
- What are the treatment options?
Cancer is common - but many cancers are not.
Improvements...

- For 2012 to 2014, the age-standardized predicted five-year net survival for all cancers combined was 63%. This was up from 55% in the early 1990s.

Oncology represents 33% of all drugs under development.
CADTH Drug Submissions

![Bar chart showing CADTH Drug Submissions from 2011 to 2019 for Oncology and Non-oncology categories.]

CADTH Drug Portfolio Information Sessions Nov 2019
Benefits are incremental, small, often unknown

Almost two-thirds of novel oncology drug indications do not achieve an overall survival or patient-reported outcome benefit.

**OS Benefit Not Found For Majority Of Novel Oncology Indications After US FDA Approval**

Date: 09 Jul 2019
Author: By Lynda Williams, Senior medwireNews Reporter
Topic: Anticancer Agents / Bioethics, Legal, and Economic Issues

medwireNews: A review of novel oncology treatments suggests that less than a third achieved an improvement in overall survival (OS) after approval by the US Food and Drug Administration (FDA).

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Results | Between 2011 and 2017, 65 drugs were approved for 71 oncology indications. For 15 of the 71 (21%) initial indications, the approval was supported by OS data (median OS gain, 1.7 months [range, 1.4-11.8 months]). For 54 of the 71 (76%) initial indications, the approval was supported by a surrogate end point (Figure 1). For indications approved based on OS data, 14 of the 15 (93%) indications were granted via traditional regulatory pathways vs 23 of the 54 (43%) indications based on surrogate end points.

Discussion | We found that the use of surrogate end points has increased in recent years (76% vs 67% during 2008-2012). For new oncology drug indications based on OS, OS gains were marginal. In the absence of OS benefit, an argument can be made that novel oncology drugs might provide patients with better quality of life. However, only a quarter of the indications showed a statistically significant improvement in PROs. More than half of the indications for oncology drugs we evaluated have not demonstrated an OS benefit nor a PRO improvement. A recent review of oncology drugs approved by the European Medicines Agency reported a similar finding. While these are encouragements, it remains to be seen if they can translate into meaningful clinical benefits for patients.
Drug prices are soaring

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

1965-2015

[Graph showing monthly and median costs of cancer drugs at the time of FDA approval from 1965 to 2015.]

A Month of Meds

Median price* of cancer drugs approved during each five-year period, for a month’s supply

$10,000

8,000

6,000

4,000

2,000

0

[Bar chart showing median prices of cancer drugs approved from 1965 to 2009.]

*initial price upon approval, in 2014 dollars

Source: Peter Bach at Memorial Sloan Kettering Cancer Center

THE WALL STREET JOURNAL.

https://www.asc.ohio-state.edu/wilkins.5/drugcost.html
Top Cancer Doctors Call for Lower Drug Costs

“It’s time for patients and their physicians to call for change”

A group of cancer doctors are joining grassroots organizers and politicians in pleading with pharmaceutical companies to reduce the cost of cancer treatments.

In an editorial that ran Thursday in the Mayo Clinic Proceedings journal, 118 cancer experts produced a series of recommendations they say would lead to a reduction in treatment expenses. The doctors say that

Cost of Cancer Drugs: Something Has To Give

The drugs often are more effective and have fewer side effects. The science—often just amazing. Medically, cancer treatment has never been in a better place. But are high prices making it unaffordable? Payers, providers, policymakers, and drugmakers themselves are wrestling with the issue. Meanwhile, many patients are being priced out of treatments that could save their lives.

“Unsustainable” Cancer Drug Prices

April 2014
By William Falcon

Over 100 oncologists are protesting the outlandish prices charged for cancer drugs and how these inflated costs are economically “unsustainable.”

Their exposé was published in a prestigious medical journal and received headline news coverage last year.

The more than 100 oncologists who authored this report noted that of twelve cancer drugs approved in 2012, eleven were priced above $100,000 per year.

Before relating the details, I ask readers to fathom who can afford $100,000 a year for one drug? This does not include hospital costs, physician fees, or other medications cancer patients typically require.
Public coverage of cancer drugs

Milton mother with two months to live devastated after OHIP fails to cover cancer treatment

By Andrew Russell
Breaking News Reporter

Cancer’s rapidly rising in Ontario—and coverage isn’t keeping pace with new treatment

Last-ditch effort for Ontario breast-cancer drug funding turned down

KAREN HOWLETT, LISA PRIEST AND TAMARA BALUJA
The Globe and Mail
Published Thursday, Mar. 10, 2011 4:10PM EST
Last updated Thursday, Aug. 23, 2012 4:56PM EDT
Public spending on cancer drugs in Ontario now exceeds $1 billion.

Ontario Public Drug Programs Spending on Cancer Drugs*

Average Annual Growth Rate =13.5% (11/12 -18/19)

*Annual expenditures are reported for IV cancer drugs (n=52) reimbursed by the New Drug Funding Program (NDFP) and take-home cancer drugs (n=91) reimbursed by the Ontario Drug Benefit Program (ODB).
†Government costs include drug costs and any associated pharmacy fees (for drugs reimbursed by ODB). Costs reported do not reflect manufacturer rebates (if applicable).
Source: ODB costs – ICES data (June 2019) ; NDFP costs – CCO data (June 2019)
Overview of cancer and the public cancer system

• Cancer drug funding
Drug funding review process

Clinical trials suggesting promise

Health Canada
Regulatory review
- Market authorization
- Is it safe to use?
- Should it be available for sale in Canada?

CADTH
Health technology assessment
- Recommendations for funding
- Does it work?
- Is it good value?
- Should we fund it?

Cancer Agencies and Ministries of Health
Implementation
- Pricing negotiations
- Funding decisions
- Can we afford it?
- Who can use it and under what circumstances?
Drug funding process - Federal

- Manufacturer-initiated
- Market authorization for a specific indication (reason for use)
- Review detailed clinical evidence, safety, manufacturing etc.
- Another federal body: Price ceiling based on external reference pricing
Drug funding process – pan-Canadian

- In-depth review and deliberation of multiple factors - benefit, value, values
- Understand impacts of a technology on patient and health system
- Inform policy decision-making for publicly-funded services
Drug funding process - Provincial

- Collaborative pricing decisions
  - One jurisdiction leads engagement for all provinces; agree to a letter of intent for common terms

- Funding decisions
  - Variation by jurisdiction whether handled by government, delegated to cancer authority, or combination

- Implementation
  - Eligibility, pathway, system, budget
Ontario drug review process

Regulatory
- Health Canada

National review
- pan-Canadian Oncology Drug Review (pCODR)
- pan-Canadian Pharmaceutical Alliance (pCPA)

Provincial review for Ontario
- Ontario submission
- Ontario Steering Committee for Cancer Drugs

Practice
- Final Decision by Executive Officer
- Ontario Public Drug Programs
- Ontario Health (Cancer Care Ontario)
- Hospitals & Patients

Ontario Health
Cancer Care Ontario
Drugs are funded from many Ontario sources

Ontario Public Drug Programs (OPDP)

- Ontario Drug Benefit (ODB)
- Trillium Drug Program
- Special Drugs Program
- Inherited Metabolic Diseases Program
- Resp. Syncytial Virus Prophylaxis

Programs Administered by OH(CCO) PDRP:

- New Drug Funding Program (CCO)
- Evidence Building Program (EBP)
- Case-by-Case Review Program (CBCRP)

Exceptional Access Program (EAP)
- Compassionate Review Policy

Private payers
Hospital budgets
Other CCO programs (QBP)

Hospital budgets
Other CCO programs (QBP)
Overview of cancer and the public cancer system

• Ontario Health (Cancer Care Ontario)
Cancer Care Ontario

- Cancer Care Ontario, now part of Ontario Health, is the Ontario government’s principal cancer advisor
- Provincial Drug Reimbursement Programs at Cancer Care Ontario administers cancer drug and service funding programs on behalf of the Ministry of Health
- The Pharmacoeconomics Research Unit provides health economics research and support to the Drug Programs and by extension to the Ministry and other stakeholders in the cancer drug funding process
Provincial Drug Reimbursement Programs and Pharmacoeconomics (PE) Research Unit

- New Drug Funding Program (NDFP)
- Evidence Building Program (EBP)
- Pharmacoeconomics Research Unit (PE) and ARCC
- Case-by-Case Review Program (CBCRP)
- Out-of-Country Program (OOC)
- PET Access Program
- Evidence Search and Review Service (ESRS)
Ontario drug review process – PDRP roles

PDRP provides system input and collaborates with partners across the process

Regulatory
- Health Canada

National review
- pan-Canadian Oncology Drug Review (pCODR)
- pan-Canadian Pharmaceutical Alliance (pCPA)

Provincial review for Ontario
- Ontario submission
- Ontario Steering Committee for Cancer Drugs

Practice
- Final Decision by Executive Officer
- Ontario Public Drug Programs
- Cancer Care Ontario
- Hospitals & Patients

Horizon scanning
- Clinician and cancer agency inputs and advice
- Implementation, adjudication, reimbursement

Submissions
- Value for money assessment
- Budgeting and forecasting
- Measurement, evaluation

Ontario Health
Cancer Care Ontario
Clinician support to system

Direct clinical engagement through Drug Advisory Committees (DAC), who provide timely evidence-based clinical and health system guidance on drug-related issues

- **Ontario Cancer Leads (OCL)** for each DAC (Breast, Gastrointestinal, Genitourinary, Gynecology, Hematology, Lung, Head Neck & Thyroid, Neuro-oncology, Skin)

- **Voluntary DAC members**

  DACs can initiate drug submissions and provide inputs throughout the drug review and implementation processes

  Members assist with horizon scanning, development of treatment algorithms, preparing proposals for consideration under the Evidence Building Program, individual case reviews and policy reviews as well as evaluation
Overview of cancer and the public cancer system

• Pharmacoeconomics Research unit: What we do and why we do it
What is pharmacoeconomics?

- A discipline to help assess the value of new therapies (often, new drugs)
- An economic evaluation considers both costs and clinical benefits of a new treatment compared to current options
- Helps ensure we use resources efficiently and achieve best possible benefits for patients

Pharmacoeconomics is crucial to ensuring value for money in our system
Pharmacoeconomics Research Unit

The Pharmacoeconomics Research unit helps the system incorporate economics into decision-making

The Pharmacoeconomics Research Unit’s work explicitly supports the guiding principles of Ontario’s public drug system, in aiming to meet the needs of Ontarians while achieving value for money with funding decisions made on the best clinical and economic evidence available

- High-quality applied economics expertise, with policy focus
- Direct clinician engagement for identification of issues, prioritization of topics, and clinical input for economic model development
- System integration (drug program and MOH) – understanding of payer perspective to ensure policy relevance of analysis and responsiveness
Where does PE Unit work fit in?

Before a drug is funded:
- Health Canada
- pan-Canadian Oncology Drug Review (pCODR)
- Ontario submission

During funding consideration:
- pan-Canadian Pharmaceutical Alliance (pCPA)
- Ontario Steering Committee for Cancer Drugs
- Final Decision by Executive Officer

After a drug is funded:
- Ontario Public Drug Programs
- Cancer Care Ontario
- Hospitals & Patients

Economic evidence for submissions
Implementation input, negotiation support
Real-world evidence of funded drugs
Pharmacoeconomics Research Unit Roles

Economic evidence is a key consideration in health technology assessment, pricing discussions and system efficiency

Before a drug is funded: Economic evidence for submissions
- Develop economic evaluations to assess cost-effectiveness and budget impact for drug funding consideration where there are clinical gaps

After a drug is funded: Real-world evidence (RWE)
- Analyse real-world data of funded therapies for ongoing monitoring and reassessment (treatment patterns, clinical outcomes, cost-effectiveness)

Support and leadership: Efficiency and sustainability
- Help decision-makers and HTA review bodies interpret complex economic evidence; support negotiations; provide policy-relevant analysis and research; inform policy directions for sustainability
Clinician-driven funding submissions

OH (CCO) facilitates prioritization and development of drug funding submissions with the clinical community to address funding gaps that will not otherwise be addressed by industry

Why?

• Funding consideration involves same rigorous requirements and review process regardless of submitter (e.g., evidence for benefit, safety, and cost-effectiveness)
• Mechanism for clinicians to remedy or clarify funding concerns of clinical interest and potential benefit to patients that are not being addressed by industry
• Enable consideration with robust, unbiased economic evidence for decision-making
• Avoids having drug funding process solely driven by manufacturer interests
• Often scenarios that are low-profit for industry (generic products, small markets)
• Promotes access to effective and cost-effective treatment options, often with small budget impact
Clinician-driven funding submissions

How?

- The PE Unit, PDRP and Ontario Cancer Leads developed a clinician-led identification and prioritization process across different tumor groups.
- Prioritize funding gaps of highest potential benefit to patients, ensuring resources are devoted to high-priority topics and supported by clinical expertise.

Impact of a novel prioritization framework on clinician-led oncology drug submissions

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G. Darling MD,*‡ S.E. Ferguson MD,*‡ A. Finelli MSc MD,*‡ T.M. Petrella MSc MD,*‡ J.R. Perry MD,*‡
K. Chan MD MSc PhD,*‡a and S. Gavura BSc(Pharm) MBA*‡a

ABSTRACT

Background  In Canada, requests for public reimbursement of cancer drugs are predominately initiated by pharmaceutical manufacturers. Clinician-led submissions provide a mechanism to initiate the drug funding process when industry does not submit a request for funding consideration. Although such requests are resource-intensive to produce, Cancer Care Ontario (Cco) has the capacity to facilitate clinician-led submissions. In 2014, cco began developing a cancer drug prioritization framework that allocates resources to systematically address a growing number of clinician-identified funding gaps with clinician-led submissions.
<table>
<thead>
<tr>
<th>Site</th>
<th>Drug Advisory Committee</th>
<th>Submitted to</th>
<th>Year assessed</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal</td>
<td>Capecitabine–oxaliplatin (XELOX) as adjuvant therapy for stage III colorectal cancer</td>
<td>OSCCD</td>
<td>2015</td>
<td>Funded under NDFP and ODB</td>
</tr>
<tr>
<td>Gynecology</td>
<td>Liposomal doxorubicin with carboplatin in ovarian cancer with platinum-sensitive occurrence</td>
<td>OSCCD</td>
<td>2017</td>
<td>Funded under NDFP</td>
</tr>
<tr>
<td>Hematology</td>
<td>Bortezomib retreatment for relapsed or refractory myeloma</td>
<td>OSCCD</td>
<td>2017</td>
<td>Funded under NDFP</td>
</tr>
<tr>
<td>Multiple&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Capecitabine for multiple evidence-informed regimens</td>
<td>OSCCD</td>
<td>2017</td>
<td>Funded under ODB as general benefit</td>
</tr>
<tr>
<td>Breast</td>
<td>Pending</td>
<td>OSCCD</td>
<td>2018</td>
<td>Pending</td>
</tr>
<tr>
<td>Hematology</td>
<td>Pending</td>
<td>OSCCD</td>
<td>2018</td>
<td>Pending</td>
</tr>
<tr>
<td>Lung</td>
<td>In progress</td>
<td>In progress</td>
<td>In progress</td>
<td>In progress</td>
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<sup>a</sup> Including gastrointestinal and breast.

OSCCD = Ontario Steering Committee for Cancer Drugs; NDFP = New Drug Funding Program; ODB = Ontario Drug Benefit.
Pharmacoeconomics in cancer

• Challenges in developing and interpreting economic evidence
The relevance of economic evaluations

pCODR recommendation outcomes  Completed reviews, 2011-2018, n=103

The “condition” that must be addressed most frequently in the conditional recommendations is the cost-effectiveness of the drug.

Trudeau et al. *JCO* 2018
DOI: 10.1200/JCO.2018.36.30_suppl.41
The relevance of economic evaluations

Value for money, in the form of cost per QALY gained, does not appear to play a role in the initial decision to reject or accept, but it was a key factor in the decision over full versus conditional approval (in non-rejected cases). There

Submissions with a higher ICER were more likely to receive a conditional than a full approval. Each $Can10,000 increase in ICER was associated with a 3.3% decrease in the likelihood of full approval. The ICER was the only statistically significant contributor to the full versus conditional approval recommendation. The impact

Skedgel et al. *Pharmaco economics* 2018

**Fig. 1** Predicted probability of full approval by incremental cost-effectiveness ratio (ICER) and final recommendation
Economics in theory vs practice

Economic evaluation as

- Decision tool
- Resource allocation
- Evidence synthesis
- Opportunity cost
Considerations in developing the economic evidence

- **Understanding the decision problem**
  - Treatment pathway, relevant comparator, place in therapy

- **Data sources**
  - Clinical trials, published sources, administrative data

- **Designing the model**
  - Model types
  - Extrapolation to lifetime outcomes
  - Exploring uncertainty
Understanding the decision problem

**Goal:** Evaluate the new treatment in comparison with the current alternatives for the same condition

**Key challenges:**
- Outdated comparators
- No comparative data (approved from single-arm data)
- Multiple comparators
- Multiple sequences – treatment pathway
Understanding the decision problem

**Goal:** Evaluate the new treatment in comparison with the current alternatives for the same condition

- Understanding current state, place in therapy ensures results are relevant to the decision problem
Understanding the decision problem

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Understanding the decision problem

**Goal:** Evaluate the new treatment in comparison with the current alternatives for the same condition

- Understanding current state, place in therapy ensures results are relevant to the decision problem
Data sources

Goal: Identify relevant and robust comparative data for all the outcomes of interest

Key challenges:

• Clinical trial data are limited
  – Small samples, non-comparative

• Clinical trial data are incomplete
  – Short follow-up, interim analysis/early termination
  – Patients who switch to the new therapy (crossover)

• Not possible to conduct some studies
Data sources

Goal: Identify relevant and robust comparative data for all the outcomes of interest

- Consider all relevant data sources to populate model

Crizotinib for advanced ROS1+ NSCLC

- ROS1-rearrangements found in ~1-2% of NSCLC cases
- Crizotinib, ALK+ targeted agent, activity against ROS1+ NSCLC
- No comparative trial evidence, small single arm studies
- Previous analyses relied on results in ALK+ population
Data sources

- Literature review: identify all relevant studies in ROS1+ NSCLC, range of outcomes
- Comparison of baseline characteristics, prior treatments, study designs
- Digitized and recreated individual-level survival times
- Evaluated uncertainty with different combinations, statistical uncertainty

<table>
<thead>
<tr>
<th>Author</th>
<th>Study Design</th>
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<tbody>
<tr>
<td><strong>Crizotinib</strong></td>
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<tr>
<td>Mazieres 2015</td>
<td>EUROS1 Retrospective study (n=31)</td>
</tr>
<tr>
<td>Shaw 2014</td>
<td>PROFILE 1001 Single-arm, multicentre, open-label phase I trial (n=50)</td>
</tr>
<tr>
<td>Wu 2018</td>
<td>Single-arm, multicentre phase II trial (n=127)</td>
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<tr>
<td><strong>Chemotherapy</strong></td>
<td></td>
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<tr>
<td>Drilon 2016</td>
<td>Retrospective study with 1L platinum + pemetrexed (n=10)</td>
</tr>
<tr>
<td>Mazieres 2015</td>
<td>EUROS1 Retrospective study, pemetrexed (alone or with platinum) (n=26)</td>
</tr>
<tr>
<td>Song 2016</td>
<td>Retrospective study with 1L palliative pemetrexed/platinum (n=12)</td>
</tr>
<tr>
<td>Zhang 2016</td>
<td>Retrospective study with pemetrexed (n=28)</td>
</tr>
<tr>
<td>Kim 2013</td>
<td>Retrospective study with pemetrexed (n=5)</td>
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Pooled survival analysis

Progression-free survival probability:

- Median PFS: Crizotinib (16.2 months), Chemo (7.8 months)
- HR: 0.47 (SE: 0.159) p-value: <0.0001
- HR in ALK+ disease: 0.48
Designing the model

**Goal:** Capture the disease pathway and all relevant events using a structure and approach appropriate for the decision problem

- Reflect current clinical or care pathway and populate with relevant data for individual’s lifetime

**Challenges:**

- Trial outcome data and model data differ
  - Require secondary sources, assumptions
- Require extrapolation beyond observed data
- Assumptions can drive the model results
Addressing challenges

- Statistical methods for indirect treatment comparisons
- Statistical methods for extrapolation, crossover adjustment
- Incorporation of external data, use of historical controls
- Sequential analysis of multiple options - incremental
  - Analyses still typically limited to single comparators rather than mix
- Emergence of partitioned survival modelling
  - Need for reasonable survival extrapolation assumptions
  - Validation, sensitivity analysis, parameter and structural uncertainty

What is most relevant to the policy decision?
What impact do assumptions have on the results?
Pharmacoeconomics in cancer

• Focus on modelling approaches: partitioned survival and Markov models
Cost-effectiveness analysis

- Compare (at least) two treatments
- What happens when using each alternative
  - Timing of events, costs and consequences
  - Estimate survival for each group (life years, quality-adjusted life years) for remaining lifetime
- Simplify disease trajectory into finite number of health states
- Key events in oncology
  - Progression (tumour growth >20%) -> Progression-free survival
  - Death -> Overall survival
Getting from clinical trial to economic model

Survival curve – proportion of cohort surviving over time

Median OS = 9 months vs. 6 months
Two modelling approaches

- Estimate survival (life years):

<table>
<thead>
<tr>
<th>Indirectly</th>
<th>Directly</th>
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<tbody>
<tr>
<td>Estimate risks of progressing from health states until reaching absorbing death state</td>
<td>Estimating (extrapolating) OS curves</td>
</tr>
<tr>
<td>Adding up time spent in the living health states</td>
<td>Adding up area-under-the-curve</td>
</tr>
</tbody>
</table>

- Markov model
- Partitioned survival analysis
Markov model

- Health states to represent different costs, quality of life, and risk
- Risks at each time point of moving to another state \((a, b, c)\)
- Patients move through time – sum to get average life years (LYs)
Partitioned survival analysis

- Directly estimate overall survival for the cohort from OS curve
- Allocate into finite number of health states to adjust for costs and quality of life
Partitioned survival analysis

- Directly estimate overall survival for the cohort from OS curve
- Allocate into finite number of health states to adjust for costs and quality of life
Estimating average survival
Proportion in health state over time

96% progression-free at 1 week
84% progression-free at 4 weeks (1 month)

Median PFS = 4.25 month
Estimating average survival
Proportion in health state over time

96% progression-free at 1 week
84% progression-free at 4 weeks (1 month)
Partitioned survival models use areas under the curves to determine time in health states.

![Graph showing survival curves for OS and PFS with time in progression and life years](image)

- OS curve
- PFS curve
- Time in:
  - Progressed state
  - Progression-free state

**Survival**

**Life years**

**Time in months**

**OS**

**PFS**

- OS curve
- PFS curve

**Ontario Health**

Cancer Care Ontario
Comparing two treatments

- Difference between survival curves (proportions) for two treatments is the difference in survival time between treatments

<table>
<thead>
<tr>
<th></th>
<th>Life years</th>
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<tbody>
<tr>
<td>New treatment</td>
<td>0.96</td>
</tr>
<tr>
<td>Comparator</td>
<td>0.73</td>
</tr>
<tr>
<td>Incremental (ΔE)</td>
<td>0.23</td>
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</table>
Pros and cons of partitioned survival models

Pros

- Aligns with trial outcomes (PFS, OS data used directly)
- Recreates observed data well
- Closely capture small differences in survival, reflect incremental gains
When not all patients experience the event at the end of trial, need to estimate what happens at later time points.
Time-to-event (also referred to as survival) analysis using parametric models can be used to extrapolate from shorter-term parameter estimates to longer-term effects. Systematic approaches to survival analysis based on individual-level data have been developed. These analyses should follow the Survival Model Selection Process Algorithm developed by the Decision Support Unit commissioned by the National Institute for Health and Care Excellence (NICE).
Extrapolating beyond observed data

- Survival analysis: Estimate the survival experience over time
- Parametric models: choose a distribution to represent different patterns for risk of event (and predict into future)
  - Hazard - rate of event at t, conditional on surviving to t
Some shapes for hazard over time
Some shapes for hazard over time

- Increasing
- Constant
- U-shaped
- Decreasing

Event rate vs. Time
Some shapes for hazard over time

- Increasing
- Constant
- U-shaped
- Decreasing

Event rate vs. Time
Some shapes for hazard over time
Some common parametric distributions

Choice related to: risk pattern (observed and beyond)

Ishak et al 2013
Different assumptions can produce very different estimates.

**Fig. 2** Illustrative survival data from a hypothetical clinical trial fitted using different parametric models.

Need for estimates to be ‘plausible’ long-term – But no formal guidance for how to evaluate
Problem when extrapolation produces unrealistic survival benefits

Median OS = 9 months vs. 6 months

People still alive after 10 years

Overall Survival

Time (months)

OS New treatment

OS Comparator
Pros and cons of partitioned survival models

Pros

- Aligns with trial outcomes (PFS, OS data used directly)
- Recreates observed data well
- Closely capture small differences in survival, reflect incremental gains

Cons

- No structural relationship between states
  - Combining multiple risks into a single estimate
- Challenging to test external validity
  - Risk of highly implausible long-term extrapolations
Problem when model produces implausible added benefits after progression

Overall Survival

Time (months)

—OS New treatment

—OS Comparator

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<thead>
<tr>
<th>Survival Time (months)</th>
<th>Life years</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.20</td>
</tr>
<tr>
<td>20</td>
<td>0.53</td>
</tr>
<tr>
<td>40</td>
<td>0.63</td>
</tr>
<tr>
<td>60</td>
<td></td>
</tr>
<tr>
<td>80</td>
<td></td>
</tr>
<tr>
<td>100</td>
<td></td>
</tr>
<tr>
<td>120</td>
<td></td>
</tr>
</tbody>
</table>

New treatment: 0.53
Comparator: 0.28

ΔE
At some point, risk pattern might change
Treatment unlikely to reduce risk indefinitely

Could assume HR=1

—OS New treatment
—OS Comparator

Life years

New treatment
Comparator

Overall Survival

Time (months)
Other distributions may be more plausible long term – Structural uncertainty from choice

![Graph showing Overall Survival over time with bars for life years comparison between New treatment and Comparator. The bars indicate a difference (Δ) of 0.13 for New treatment and 0.42 for Comparator.](#)
Benefits of Markov models

- Control where risks differ and where treatment effects occur
  - New treatment can have lower risk of progression than comparator, but same risks of death as the comparator after progression

A) Risk of progression

B) Risk of death while progression-free

C) Risk of death after progression
So what’s the difference?

- Data needed (three risks vs. two curves)
- Assumptions needed (how risks change over time)

**Progression-free**

- **a)** Risk of progression

**Progressed**

- **b)** Risk of death while progression-free

**Dead**

- **c)** Risk of death after progression

$PFS$  
$1-OS$
Do Markov models address concerns related to partitioned survival models?

- Markov models explicitly specify risks from each state
  - Account for changes in risk from progression
  - Can control where treatment effects occur and test alternatives

- But with different data and assumptions
  - Data for (C) not reported in trials – Use external data, assume equal risks, often assuming no time-dependence for this probability
  - Implicit assumptions in extrapolations, difficult to assess external validity – Risk of highly implausible long-term extrapolations
NICE DSU TECHNICAL SUPPORT DOCUMENT 19:
PARTITIONED SURVIVAL ANALYSIS FOR DECISION MODELLING IN
HEALTH CARE: A CRITICAL REVIEW

REPORT BY THE DECISION SUPPORT UNIT

2 June 2017

Beth Woods¹, Eleftherios Sideris¹, Stephen Palmer¹, Nick Latimer², Marta Soares¹

PharmacoEconomics
DOI 10.1007/s40273-017-0583-4

CURRENT OPINION

Oncology Modeling for Fun and Profit! Key Steps for Busy Analysts in Health Technology Assessment

Jaclyn Beca¹ · Don Huseaue²,³ · Kelvin K. W. Chan⁴,⁵ · Neil Hawkins⁶ · Jeffrey S. Hoch⁷
Case study

- Bevacizumab + capecitabine (new strategy) vs. capecitabine alone (comparator) for first line metastatic colorectal cancer
- Developed 3 state partitioned survival and 3 (also 4 and 5) state Markov model
- Fit parametric distributions to recreated trial survival data (AVEX)
  - PFS for both models and OS for partitioned survival
- Assumed same risk after progression regardless of initial treatment strategy for Markov transition probabilities
Survival curve fitting - PFS

KM data digitized using Engauge software from Cunningham et al 2013
Validation of the Markov model - OS

KM data digitized using Engauge software from Cunningham et al 2013
Partitioned survival analysis OS

KM data digitized using Engauge software from Cunningham et al 2013
Comparing incremental results

<table>
<thead>
<tr>
<th></th>
<th>Markov</th>
<th>Partitioned</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Costs</td>
<td>$53,902</td>
<td>$53,209</td>
</tr>
<tr>
<td>PFS</td>
<td>$54,115</td>
<td>$54,115</td>
</tr>
<tr>
<td>Progressed</td>
<td>-$213</td>
<td>$906</td>
</tr>
<tr>
<td>Total Life Years</td>
<td>0.313</td>
<td>0.216</td>
</tr>
<tr>
<td>PFS</td>
<td>0.343</td>
<td>0.343</td>
</tr>
<tr>
<td>Progressed</td>
<td>-0.030</td>
<td>-0.127</td>
</tr>
<tr>
<td>Total QALYs</td>
<td>0.245</td>
<td>0.186</td>
</tr>
<tr>
<td>PFS</td>
<td>0.263</td>
<td>0.263</td>
</tr>
<tr>
<td>Progressed</td>
<td>-0.018</td>
<td>-0.077</td>
</tr>
<tr>
<td>ICER $ / LY Gained</td>
<td>$172,295</td>
<td>$246,302</td>
</tr>
<tr>
<td>ICER $ / QALY Gained</td>
<td>$220,027</td>
<td>$286,121</td>
</tr>
</tbody>
</table>

- Difference between OS curves in the trial was smaller than that for PFS
  - PFS not perfect surrogate
- Markov assumptions did not include difference in risk after progression
- Sufficient OS data to extrapolate and produce plausible outcomes ***
Implications

• The two methods make different assumptions
  – How (or whether) risks change over time
  – Where treatment effects are applied

• Both uncertain when based on limited observed data
  – Benefits of undertaking multiple approaches
  – Additional methods may address some of these issues: Incorporating external data, flexible models, multi-state models, calibration
  – Ongoing research need

• Importance of assessing uncertainty, impact of assumptions
  – Understand possible outcomes (not necessarily “right” answer)
Summary and future directions
Where is the field going?

• Continuously evolving techniques
  – Concerns with partitioned survival models arise from application (justified when using implausible extrapolations from immature data)
  – Better ways to extrapolate into the future, and best practice research
  – Incorporating structural uncertainty

• Additional challenges
  – Basket trials (non-comparative + multiple cancers), curative therapies
  – Growing importance of estimates on policy

• Health technology management
  – Can deal with uncertainty, but at risk of kicking the can down the road
  – Conditional listing, reassessment, real world evidence

www.cc-arcc.ca/canrevalue
To sum up

• Growing need in cancer
  – Higher incidence, prevalence
  – Lots of different cancers – types and subtypes
  – Active pipeline of discovery, development

• Difficult decisions
  – Most systemic treatment benefits are incremental, non-curative
  – Very high cost
  – Patient impact
To sum up

• Multifaceted assessment

• Detailed expertise and input across the spectrum
  – Close clinical engagement given complexity of evidence and practice

• Pharmacoeconomics methods and expertise crucial to ensuring value for money

• Pharmacoeconomics Research Unit helps system incorporate economics into decision making
  – One role is to develop evidence needed to consider drugs for funding and ensure the evidence is useful: addresses decision problem, synthesizes all available evidence, and explores assumptions and uncertainties to provide the best evidence
To sum up

- **Major challenges in oncology**
  - Making relevant comparisons is increasing difficult as treatment landscapes become more complex and rapidly evolving
  - Data are becoming more limited with smaller evidence base, shorter follow up and residual uncertainties from immature data
  - Evolution in modelling techniques from emphasis on survival analysis and extrapolation; guidance still catching up

  **What is most relevant to the decision?**

  **What impact do assumptions have on the results?**

- **Appreciation of and need for managing uncertainty**
  - Technical – techniques and guidance
  - Policy – thoughtful planning, opportunity cost -> patient outcomes
Thank you

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