Economic evaluations for cancer drug reimbursement policy-making in practice

My views from the Pharmacoeconomics Research Unit

JACLYN BECA, MSC

CCHE SEMINAR | JANUARY 2020

Ontario Health
Cancer Care Ontario

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

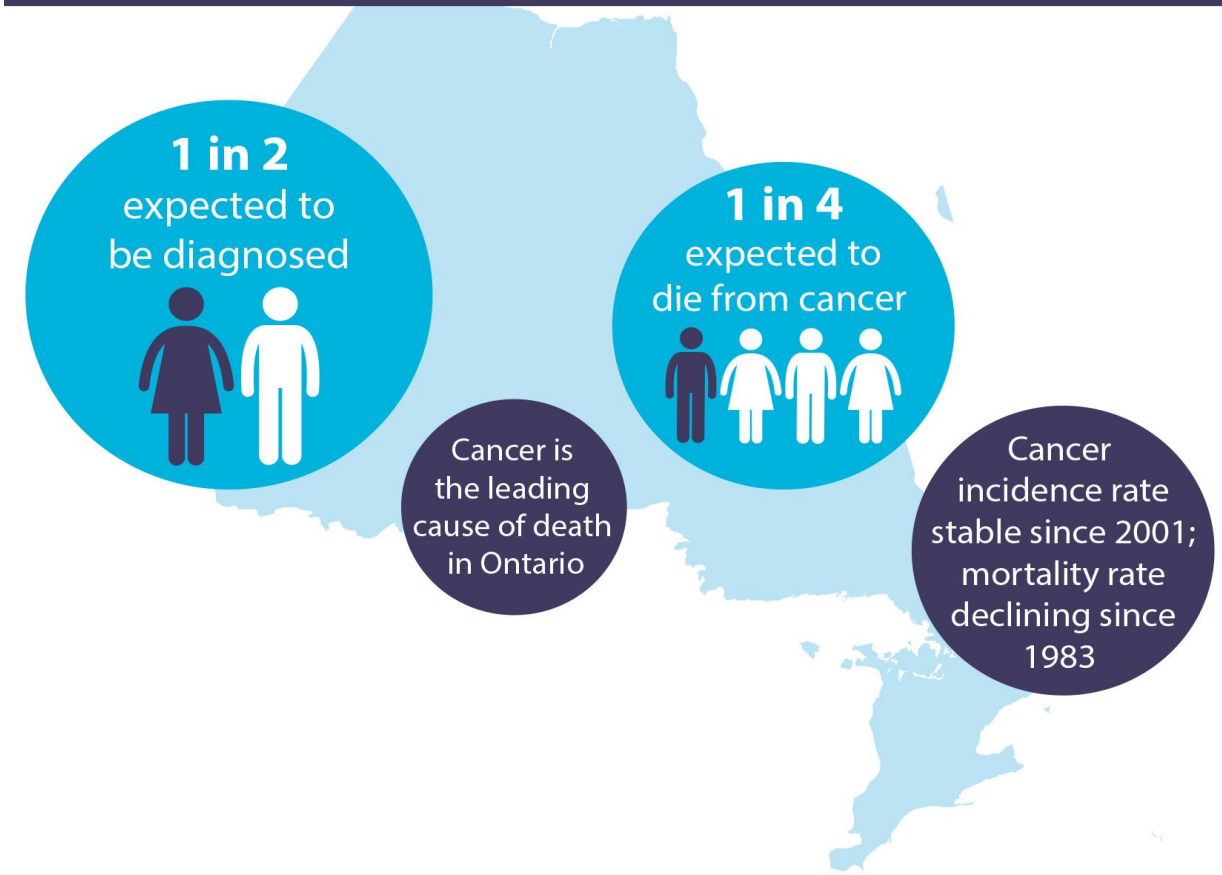
Overview of cancer and the public cancer system

- Cancer

Cancer

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

Cancer in Ontario



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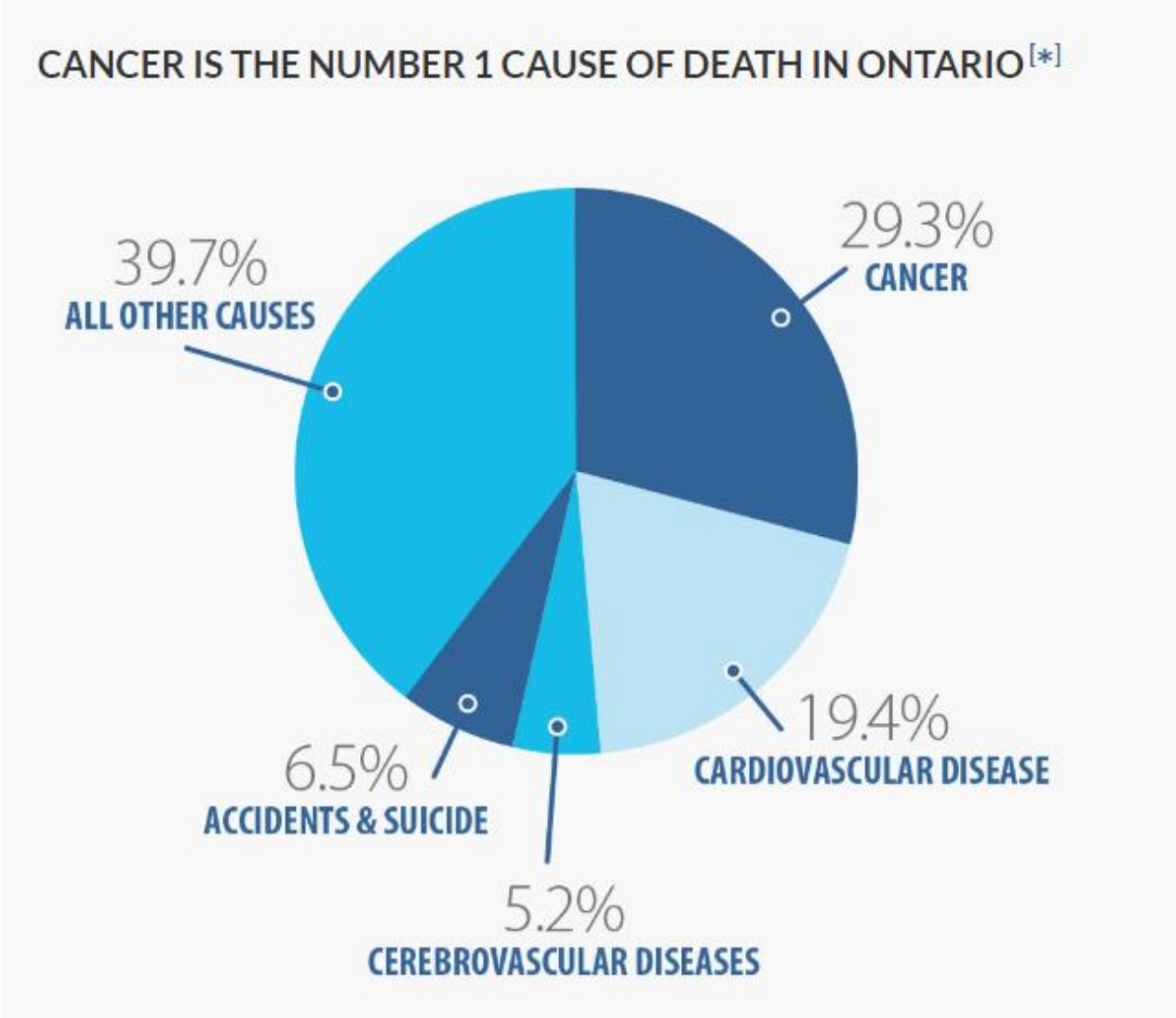
Cancer



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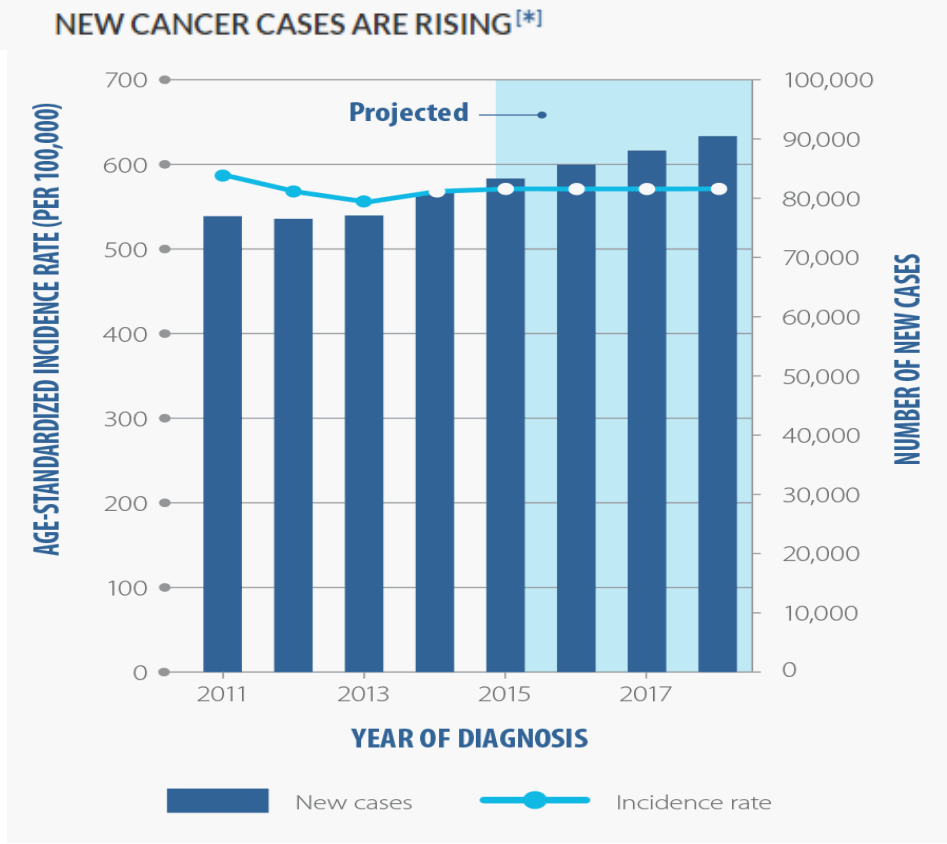
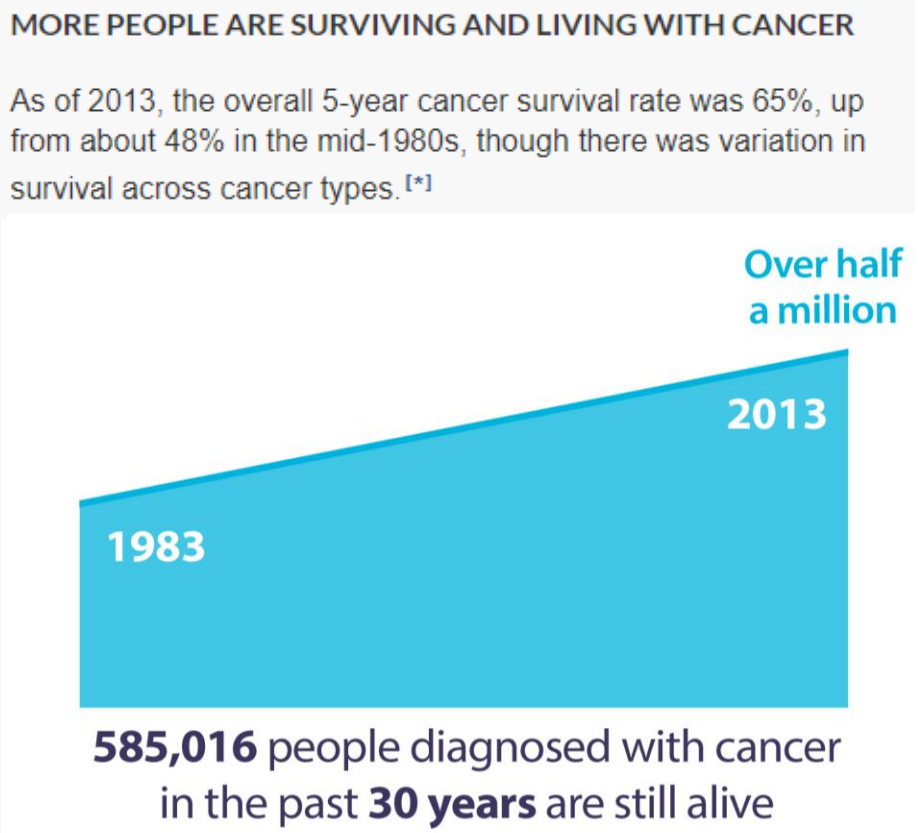
https://www.cancercareontario.ca/en/cancerplan

Increased incidence and prevalence





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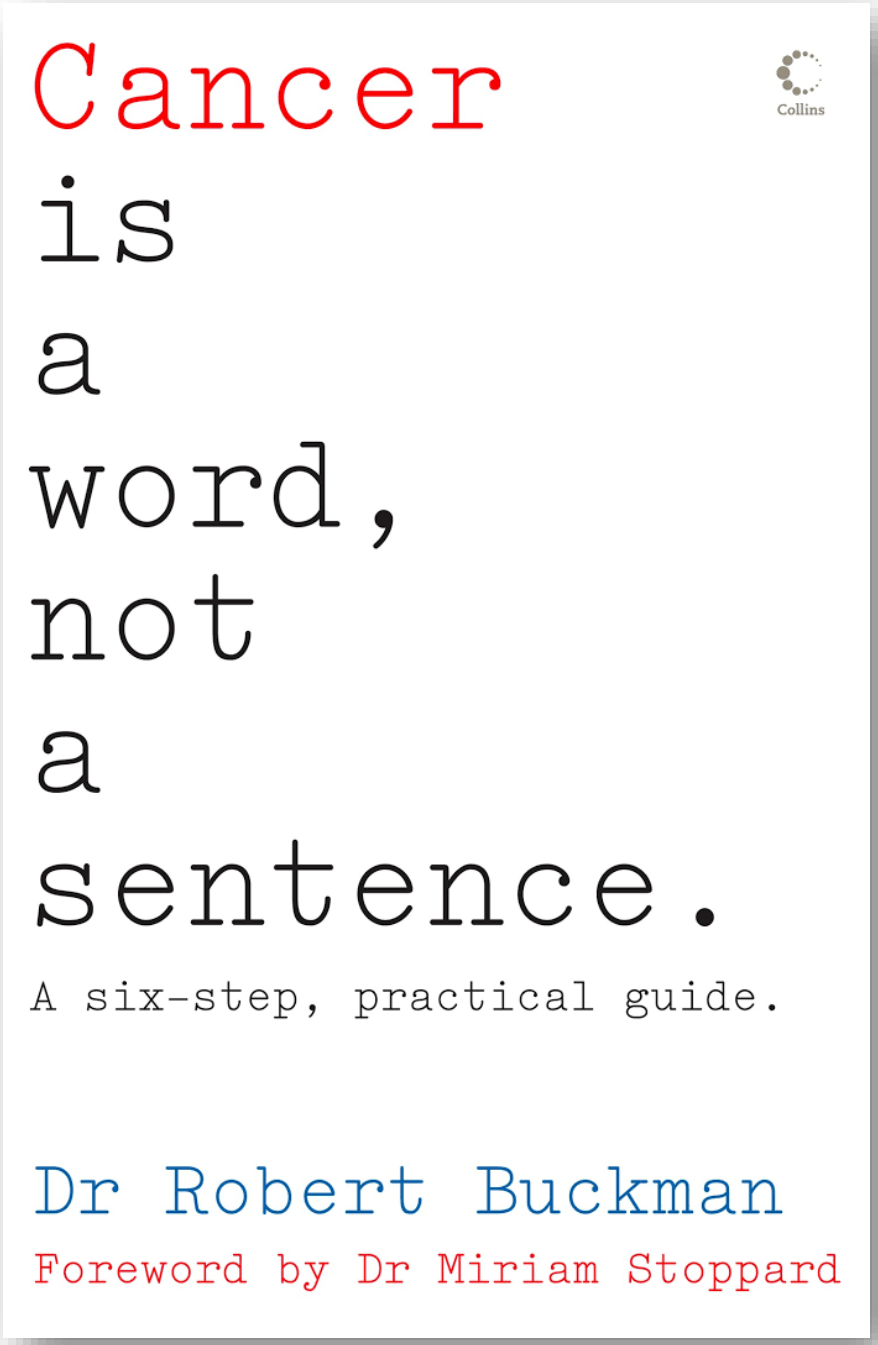

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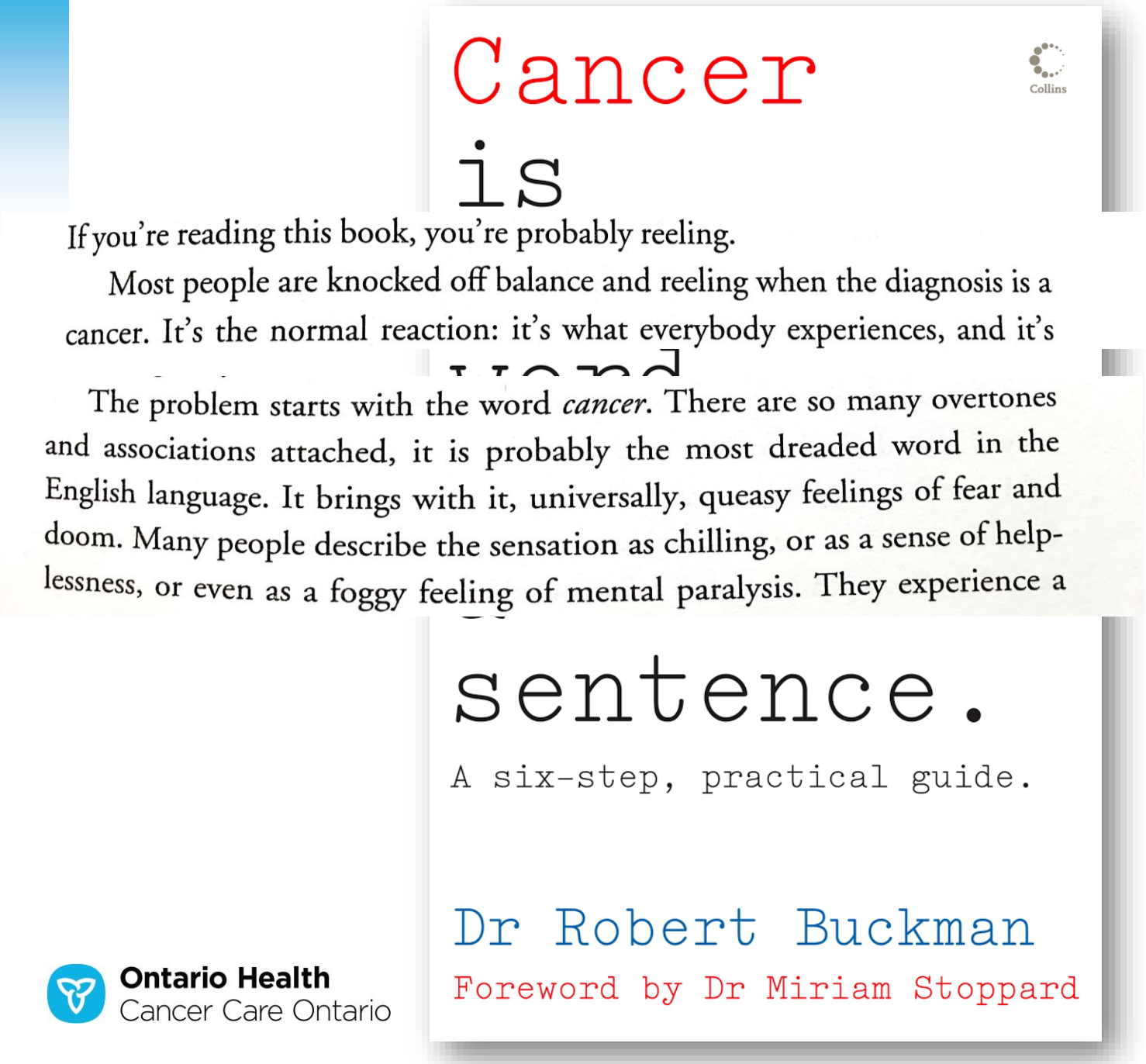


Ontario Health
Cancer Care Ontario

Cancer is

Collins

title. 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:

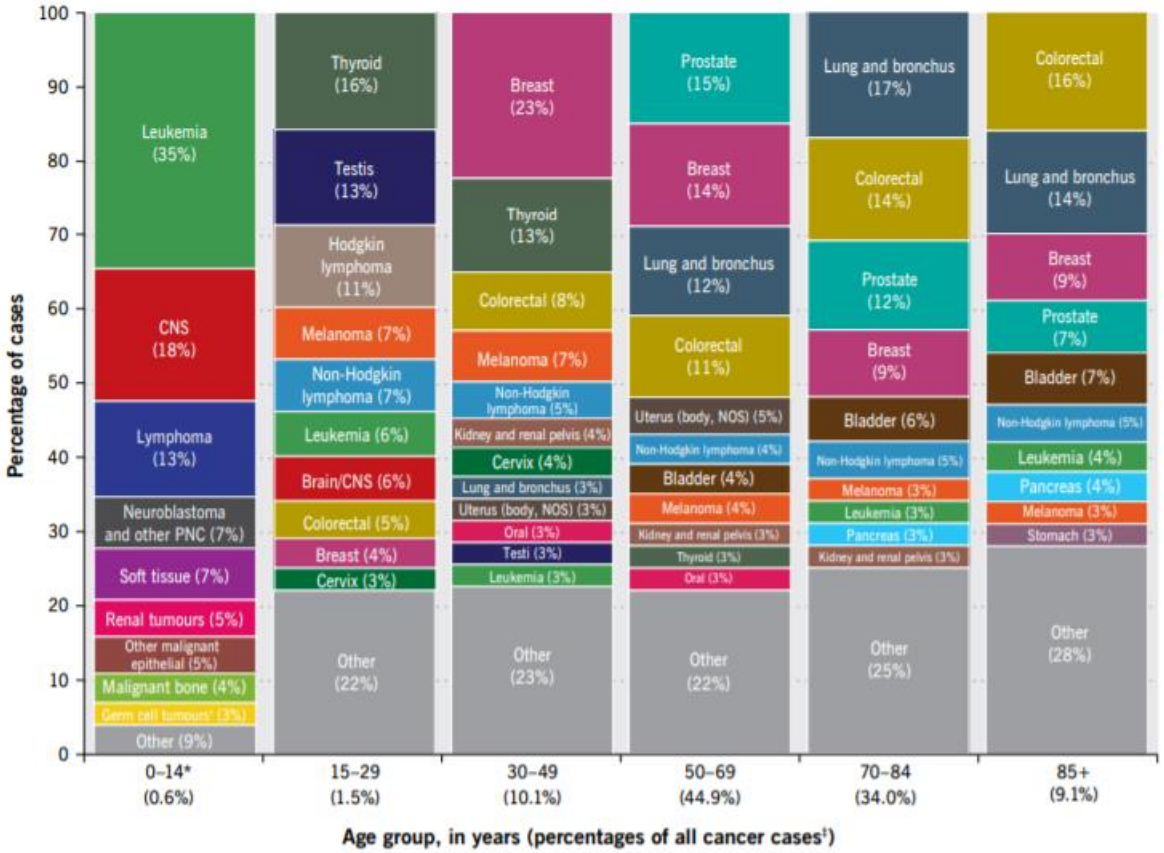
- What specific disease – which of the two hundred different cancers – is it?
- What does it actually mean for your future?
- How does this particular cancer behave?
- What are the treatment options?

Dr Robert Buckman

Foreword by Dr Miriam Stoppard

Cancer is common - but many cancers are not

FIGURE 1.4 Distribution of new cancer cases for selected cancers, by age group, Canada (excluding Quebec), 2011–2015

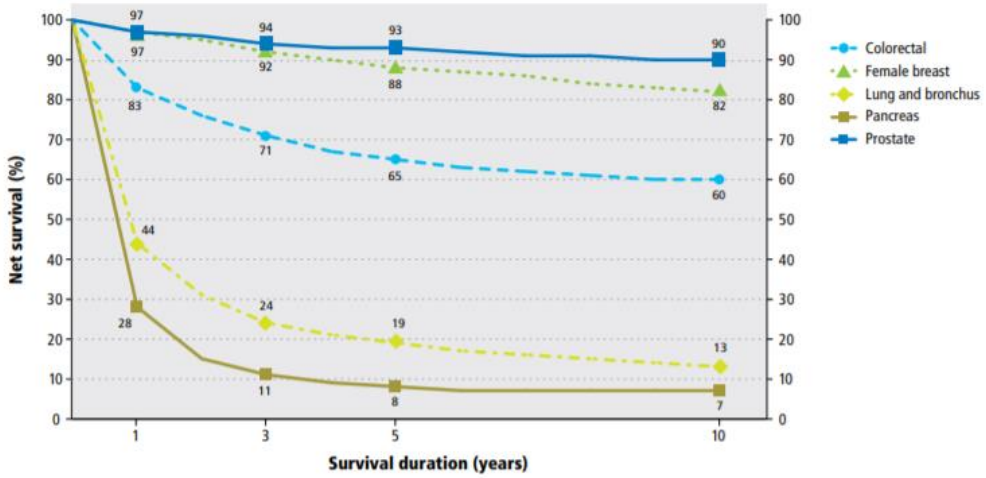


Canadian Cancer Statistics, 2019 : cancer.ca/Canadian-Cancer-Statistics-2019-EN

Improvements…

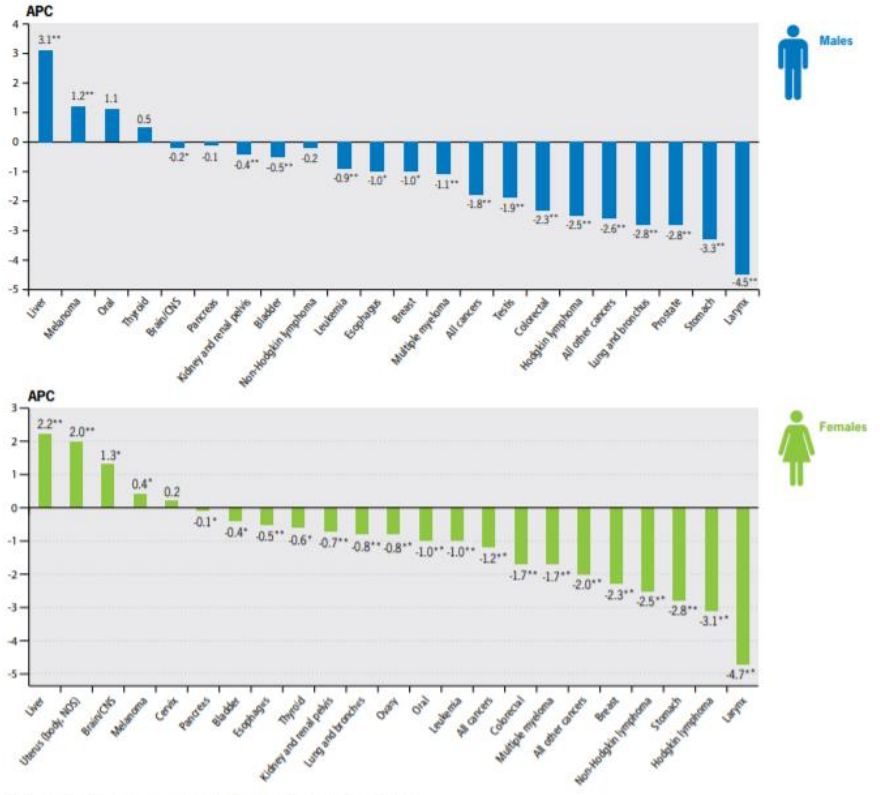
- For 2012 to 2014, the age-standardized predicted five-year net survival for all cancers combined was 63%. This was up from 55% in the early 1990s.

FIGURE 3.1 Predicted net survival for leading causes of cancer death by survival duration, ages 15–99, Canada (excluding Quebec*), 2012–2014



Analysis by: Centre for Population Health Data, Statistics Canada
Data sources: Canadian Cancer Registry death linked file (1992–2014) and life tables at Statistics Canada

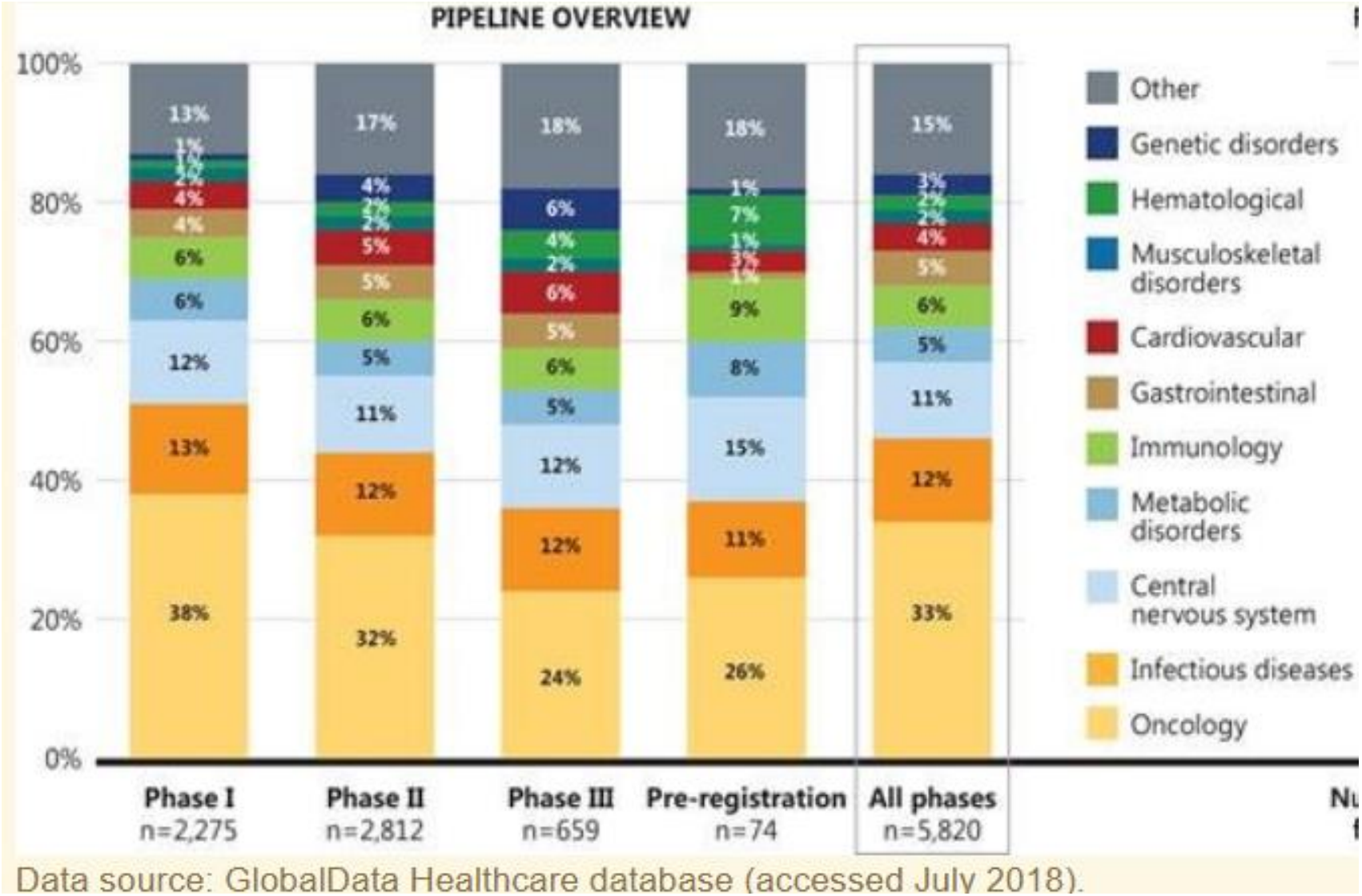
FIGURE 2.7 Most recent annual percent change (APC)† in age-standardized mortality rates (ASMR), by sex, Canada, 1984–2015



CNS=central nervous system; NOS=not otherwise specified
* APC differs significantly from 0, p<0.05
** APC differs significantly from 0, p<0.001

Canadian Cancer Statistics, 2019 : cancer.ca/Canadian-Cancer-Statistics-2019-EN

Oncology represents 33% of all drugs under development



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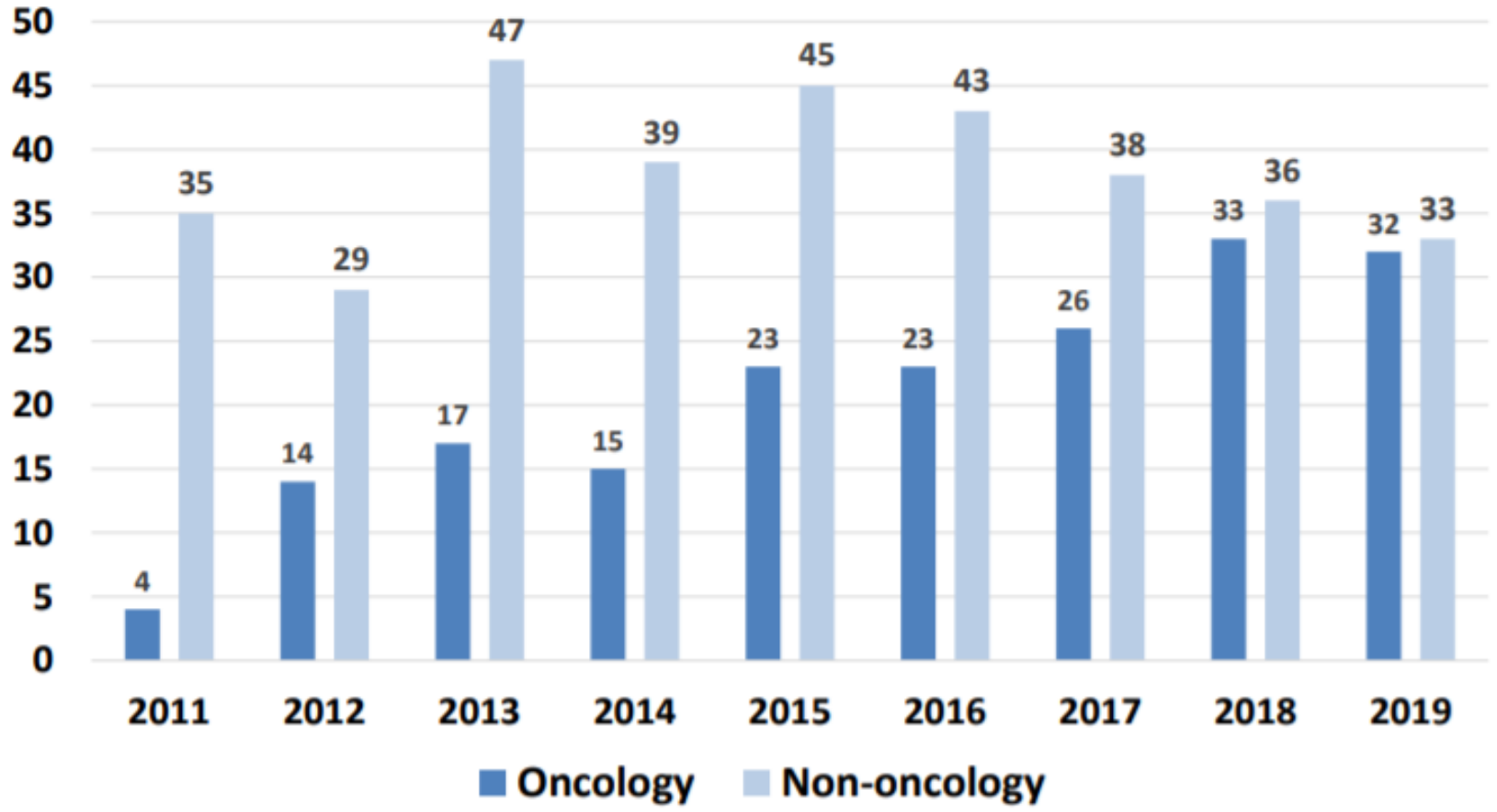
Meds Pipeline Monitor 2018 http://www.pmprb-cepmb.gc.ca/view.asp?ccid=1457&lang=en#snapshot

CADTH Drug Submissions



CADTH

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CADTH Drug Portfolio Information Sessions Nov 2019
https://www.cadth.ca/sites/default/files/events/Drug%20Portfolio%20Info%20Session%20-%202019%20-%20Consolidated%20Deck%20-%20FINAL.pdf

Benefits are incremental, small, often unknown

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

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

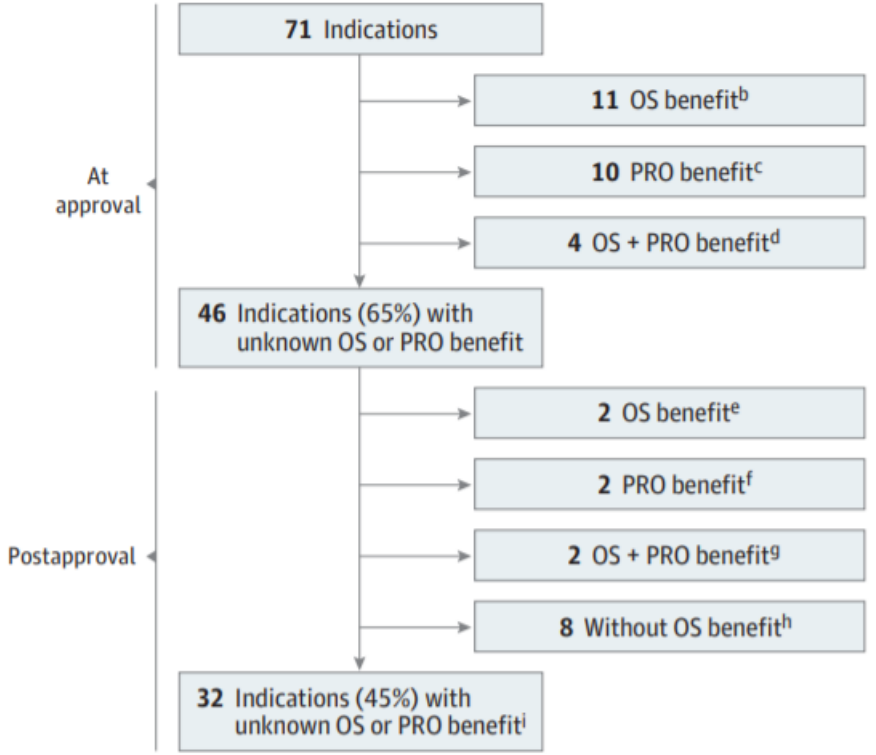
Date: 09 Jul 2019

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).

Figure 2. OS and PRO Benefits for 71 Initial Indications of 65 Novel Oncology Drugs Approved by the FDA Between 2011 and 2017[a]



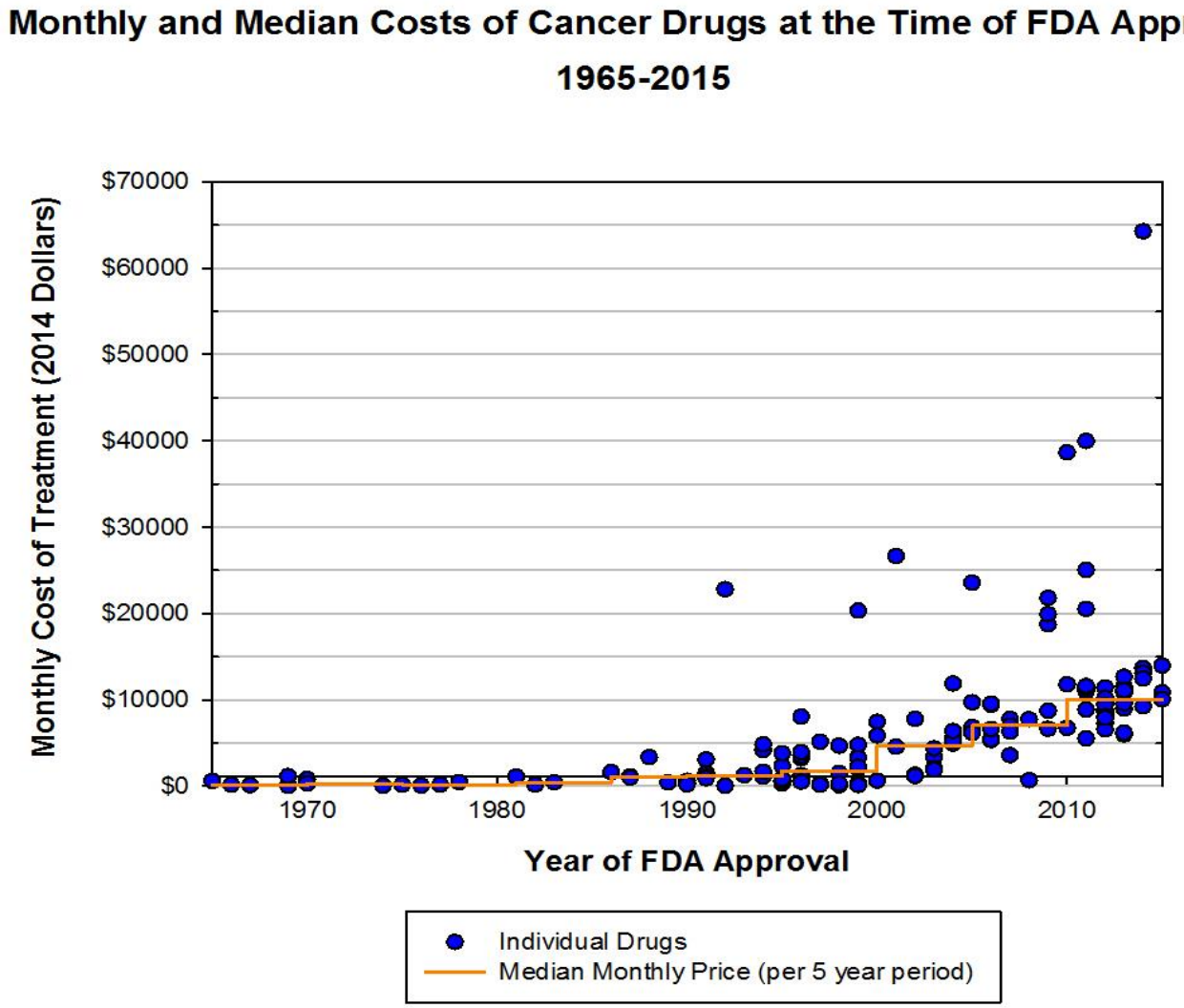
Zettler et al. *JAMA Oncol*; 2019. doi:10.1001/jamaoncol.2019.1760

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.

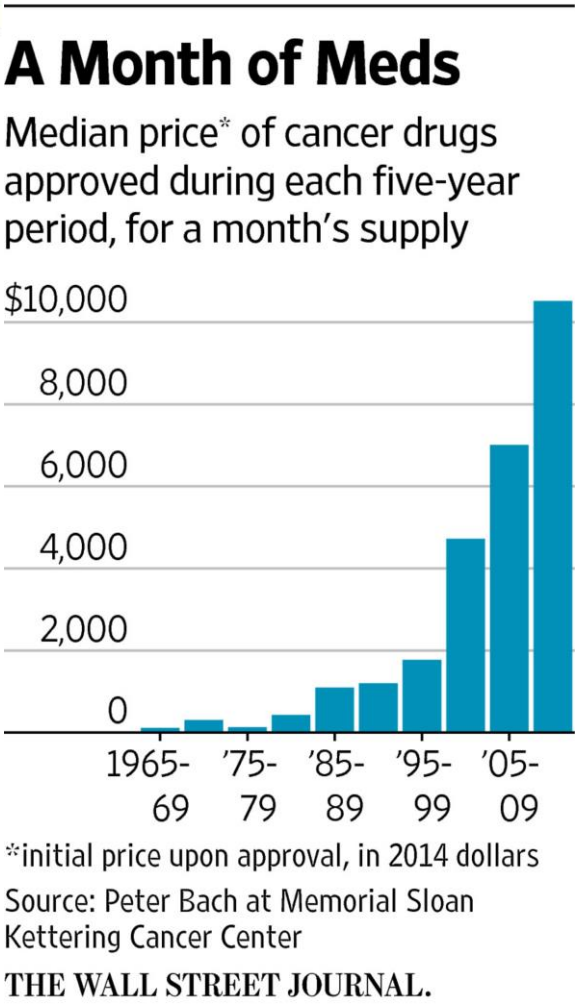
Discussion | We found that the use of surrogate end points has increased in recent years (76% vs 67% during 2008-2012).[4] For new oncology drug indications based on OS, OS gains were marginal. In the absence of OS benefit, an argument can be made that novel oncology drugs might provide patients with 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.[5] While

Drug prices are soaring



Source: Peter B. Bach, MD, Memorial Sloan-Kettering Cancer Center



https://www.asc.ohio-state.edu/wilkins.5/drugcost.html

Ontario Health
Cancer Care Ontario

HEALTH CANCER

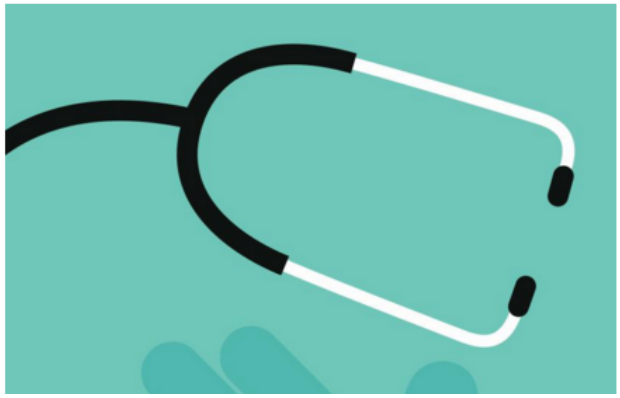
Top Cancer Doctors Call for Lower Drug Costs

Maya Rhodan @m_rhodan | July 23, 2015

"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



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.

May 3, 2018

ERIC BENDER

"Unsustainable" Cancer Drug Prices

April 2014

By William Faloon

Over **100 oncologists** are protesting the outlandish prices charged for **cancer drugs** and how these inflated costs are economically "***unsustainable***."[1]

Their exposé was published in a prestigious medical journal and received **headline news** coverage last year.[1,2]

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**.[1]

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

HEALTH October 26, 2013 6:57 pm Updated: October 29, 2013 11:43 am

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

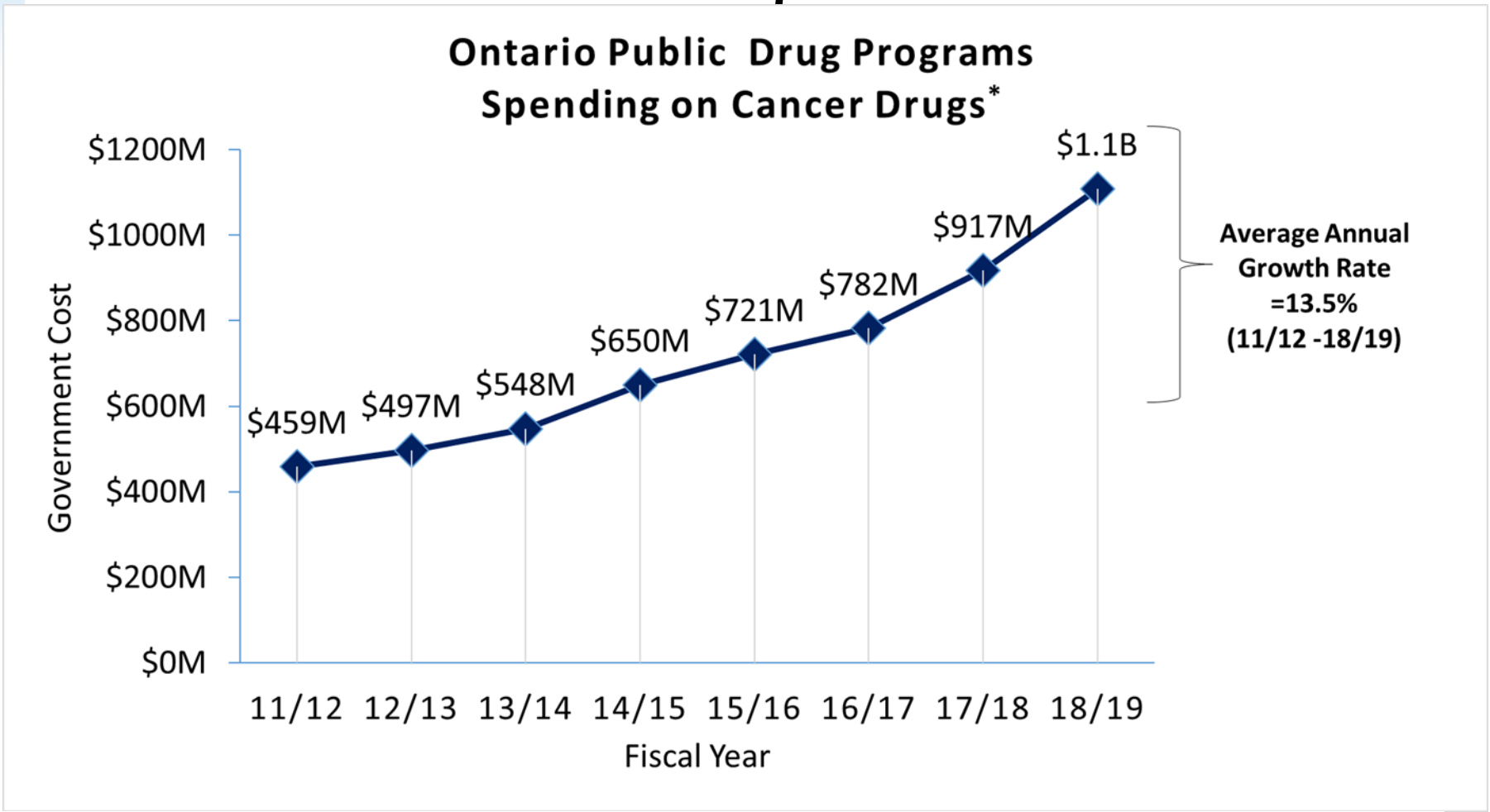
By Andrew Russell
Breaking News Reporter

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



*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

Patented Medicine Prices Review Board
Conseil d'examen du prix des médicaments brevetés

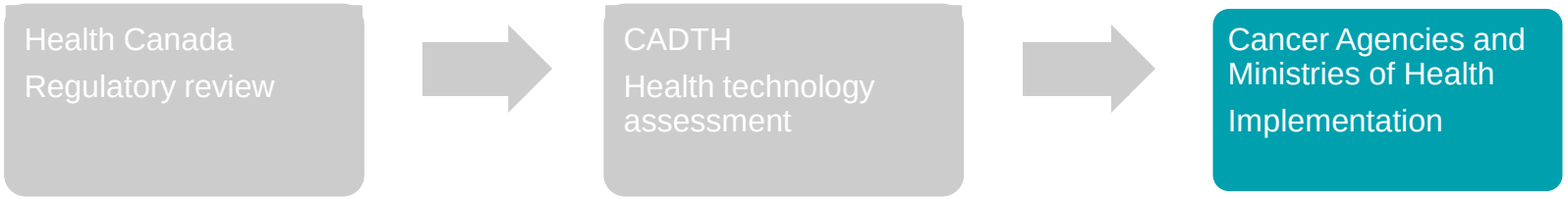
Drug funding process – pan-Canadian

- 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

pERC's *Deliberative Framework* for drug funding recommendations focuses on four main criteria:

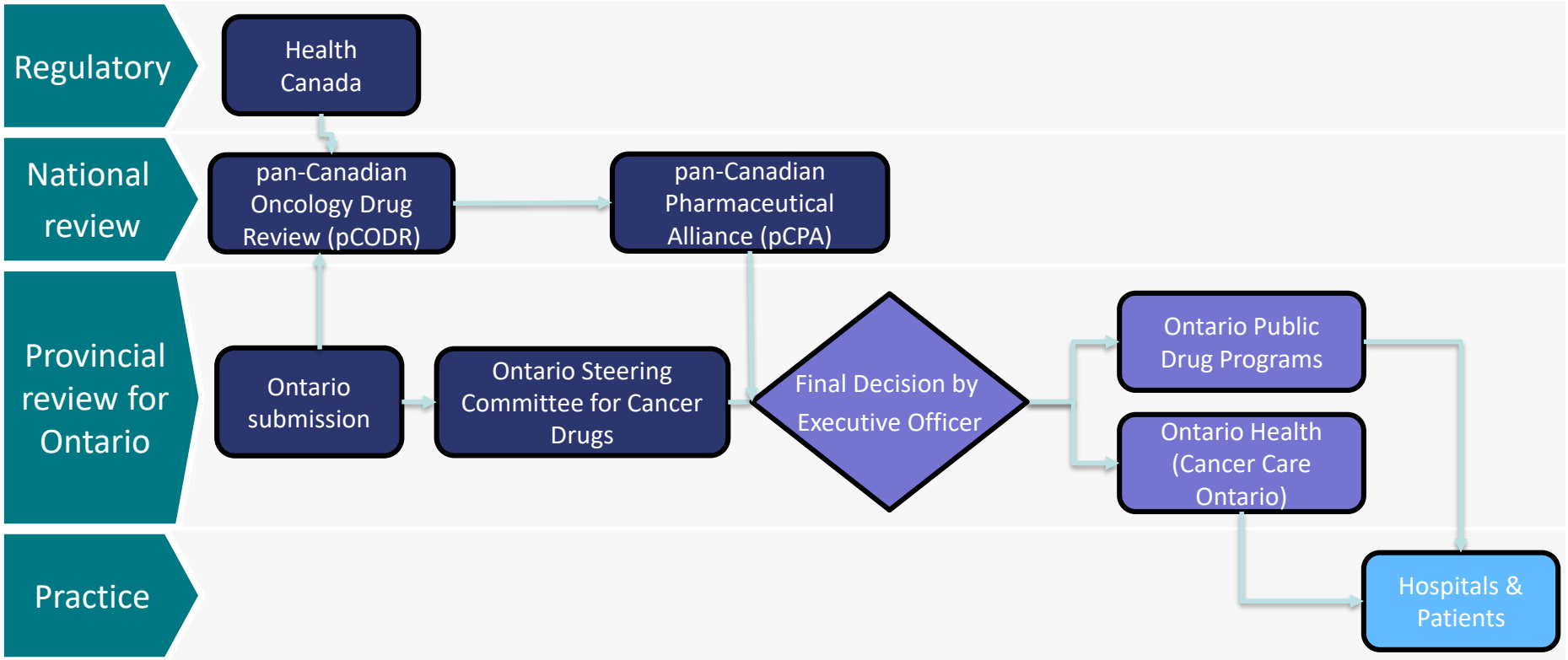
CLINICAL BENEFIT	PATIENT-BASED VALUES
ECONOMIC EVALUATION	ADOPTION FEASIBILITY

Drug funding process - Provincial

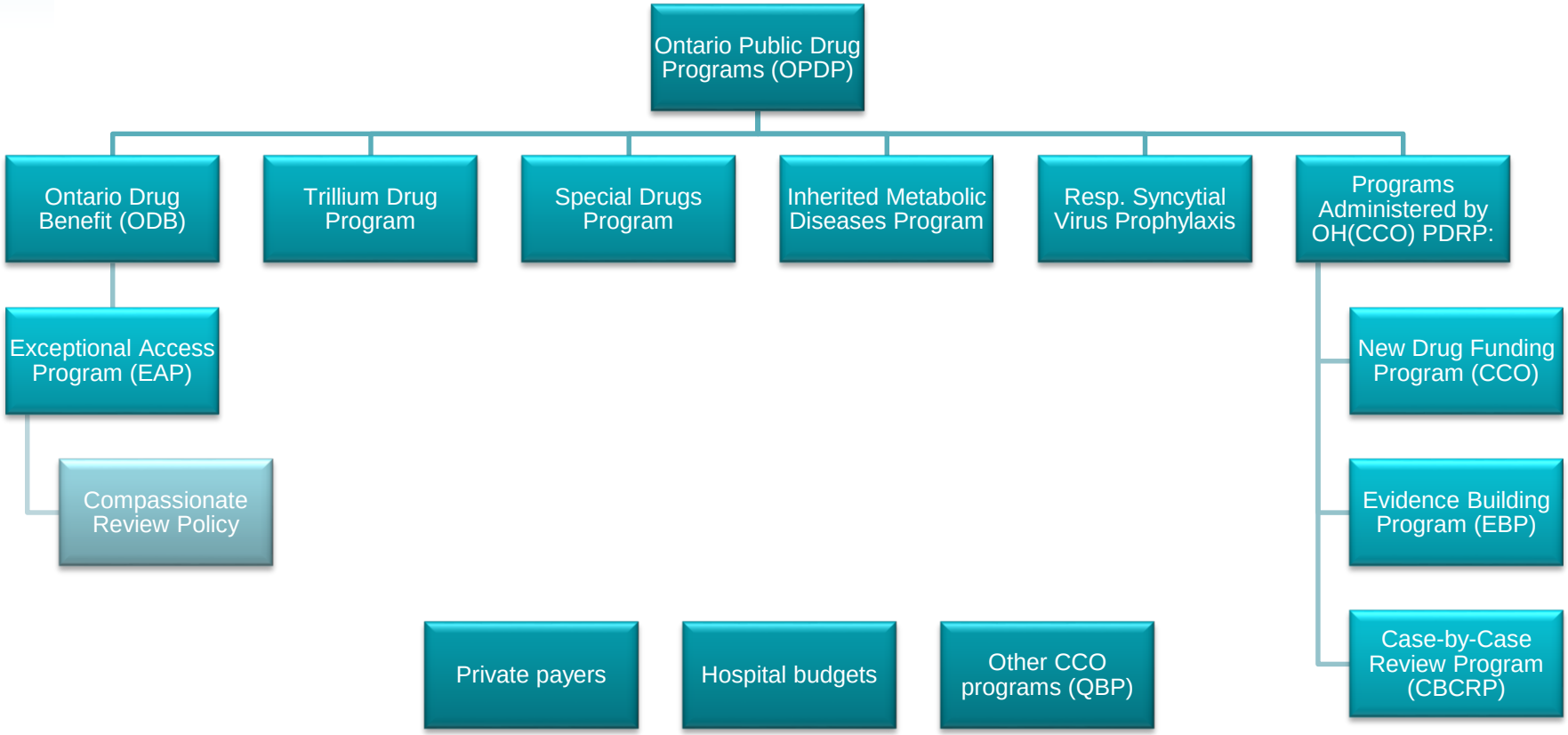


- Collaborative pricing decisions
  - One jurisdiction leads engagement for all provinces; agree to a letter of intent for common terms
- Funding decisions
  - Variation by jurisdiction whether handled by government, delegated to cancer authority, or combination
- Implementation
  - Eligibility, pathway, system, budget

Ontario drug review process



Drugs are funded from many Ontario sources



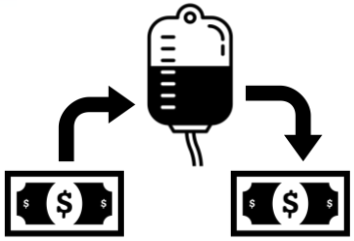
Overview of cancer and the public cancer system

- 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)

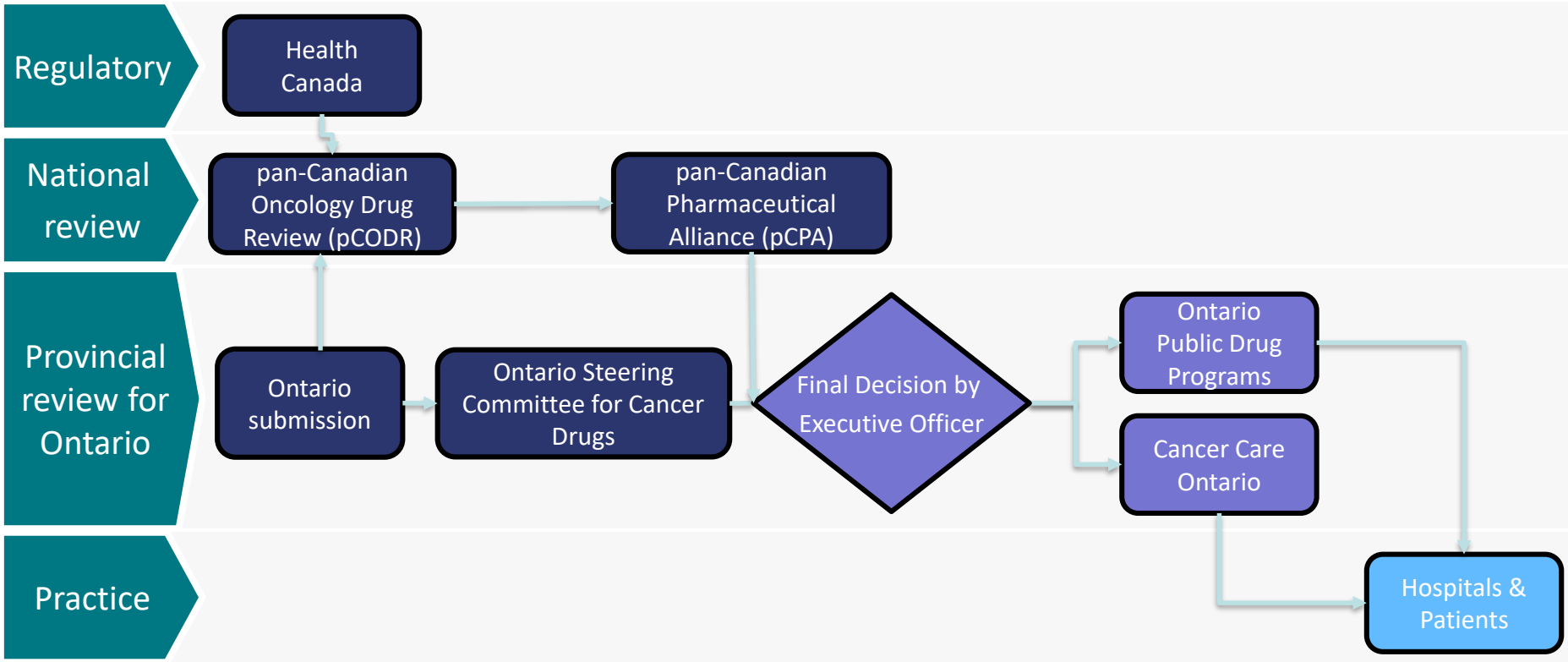
Out-of-Country Program (OOC)

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



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

Submissions | **Value for money assessment** | **Budgeting and forecasting** | **Measurement, evaluation**

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

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

55 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

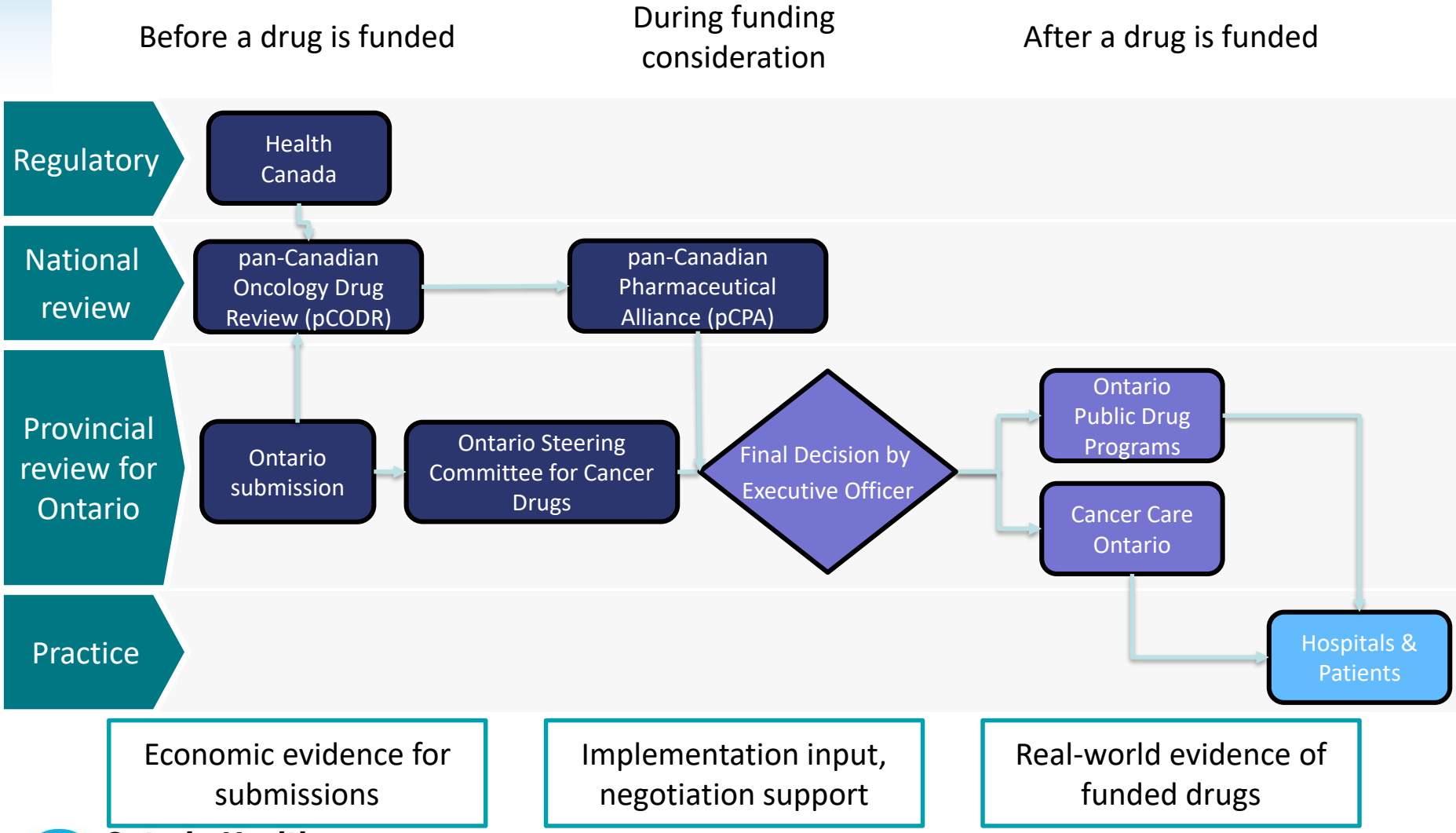
Pharmacoeconomics Research Unit

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?



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

CURRENT ONCOLOGY
A Canadian Cancer Research Journal

ORIGINAL ARTICLE

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

J. Keech,*† J. Beca MSc,*† A. Eisen MD,*‡ E. Kennedy MD PhD,*§ J. Kim MD,*# C.T. Kouroukis MSc MD,*||
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 III Clinician-led submissions to Cancer Care Ontario's Drug Advisory Committee since 2015

Drug Advisory Committee		Submitted to	Year assessed	Status
Site	**Funding request**			
Gastrointestinal	Capecitabine–oxaliplatin (XELOX) as adjuvant therapy for stage III colorectal cancer	OSCCD	2015	Funded under NDFP and ODB
Gynecology	Liposomal doxorubicin with carboplatin in ovarian cancer with platinum-sensitive occurrence	OSCCD	2017	Funded under NDFP
Hematology	Bortezomib retreatment for relapsed or refractory myeloma	OSCCD	2017	Funded under NDFP
Multiple[a]	Capecitabine for multiple evidence-informed regimens	OSCCD	2017	Funded under ODB as general benefit
Breast	Pending	OSCCD	2018	Pending
Hematology	Pending	OSCCD	2018	Pending
Lung	In progress	In progress	In progress	In progress

[a] Including gastrointestinal and breast.

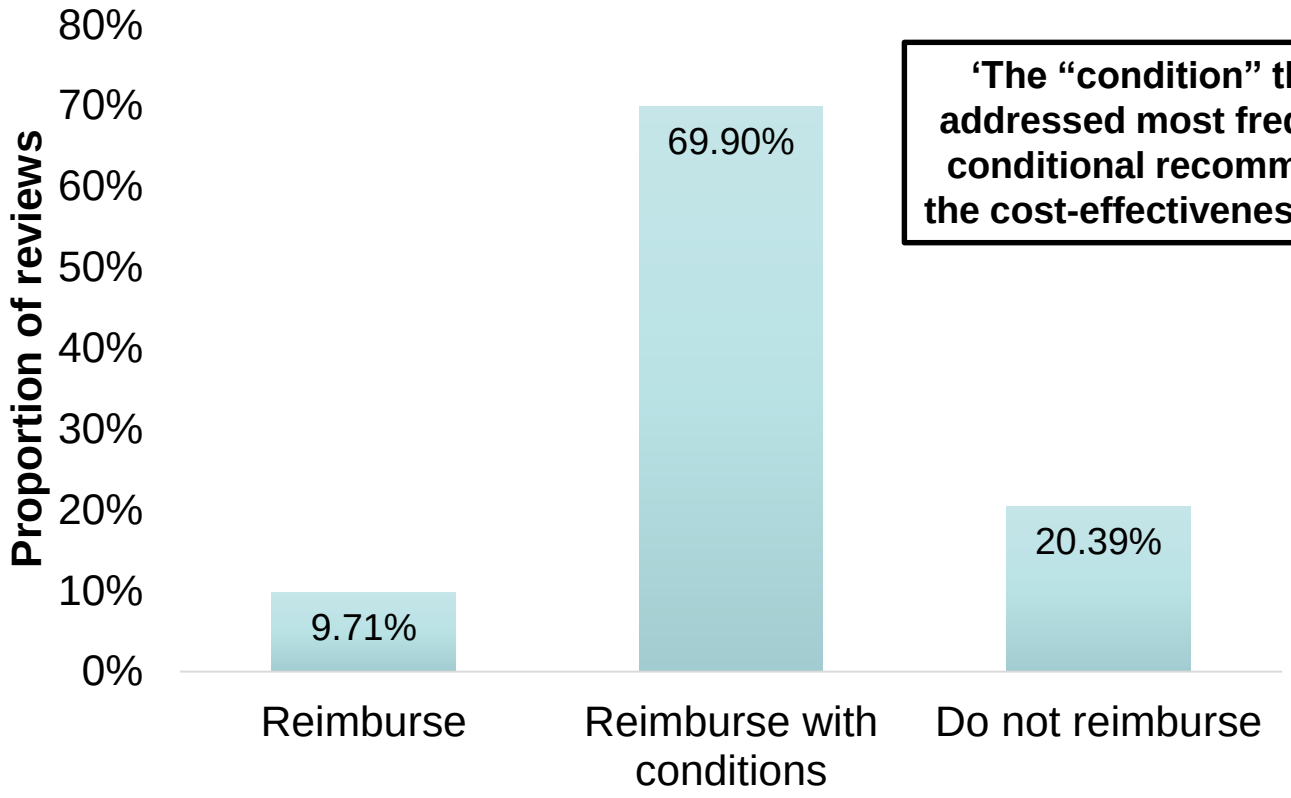
OSCCD = Ontario Steering Committee for Cancer Drugs; NDFP = New Drug Funding Program; ODB = Ontario Drug Benefit.

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.'

Ontario Health
Cancer Care Ontario

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

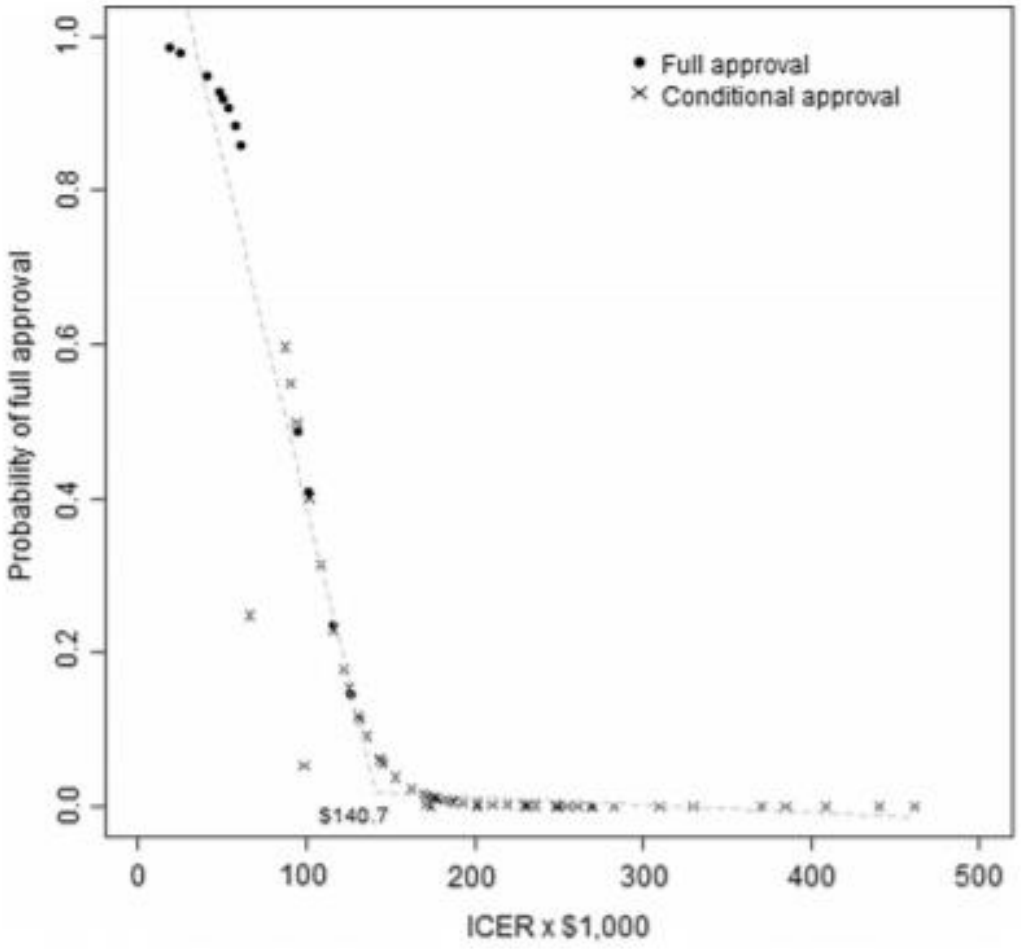


Fig. 1 Predicted probability of full approval by incremental cost-effectiveness ratio (ICER) and final recommendation

Skedgel et al. *Pharmacoeconomics* 2018

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

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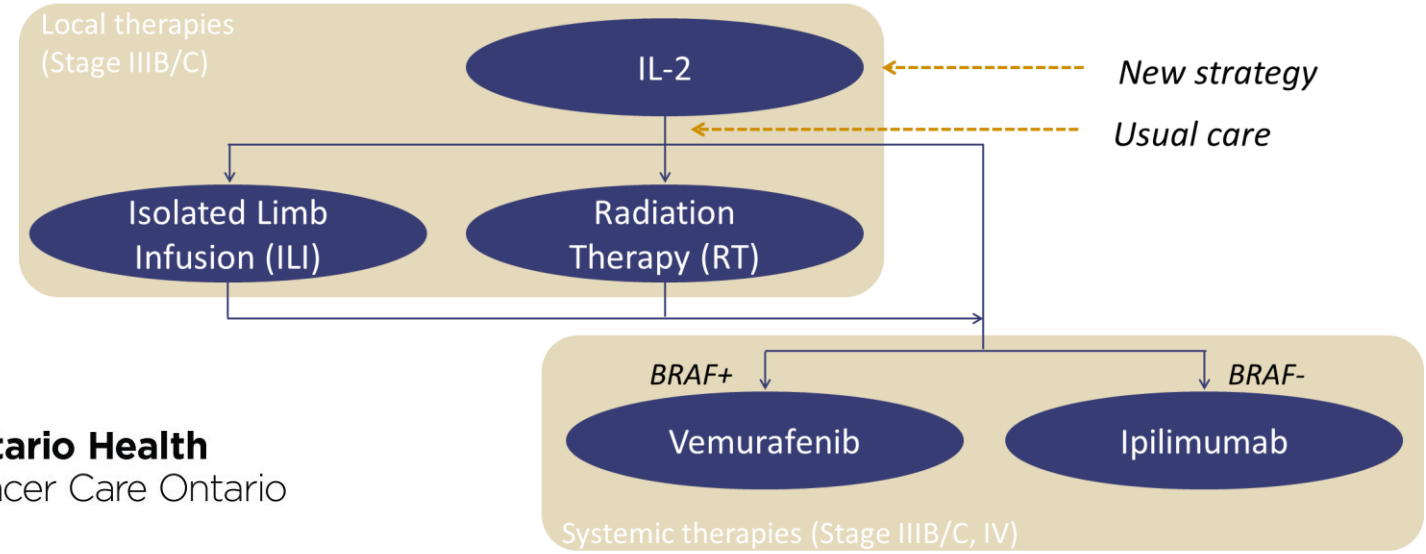


Data sources

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

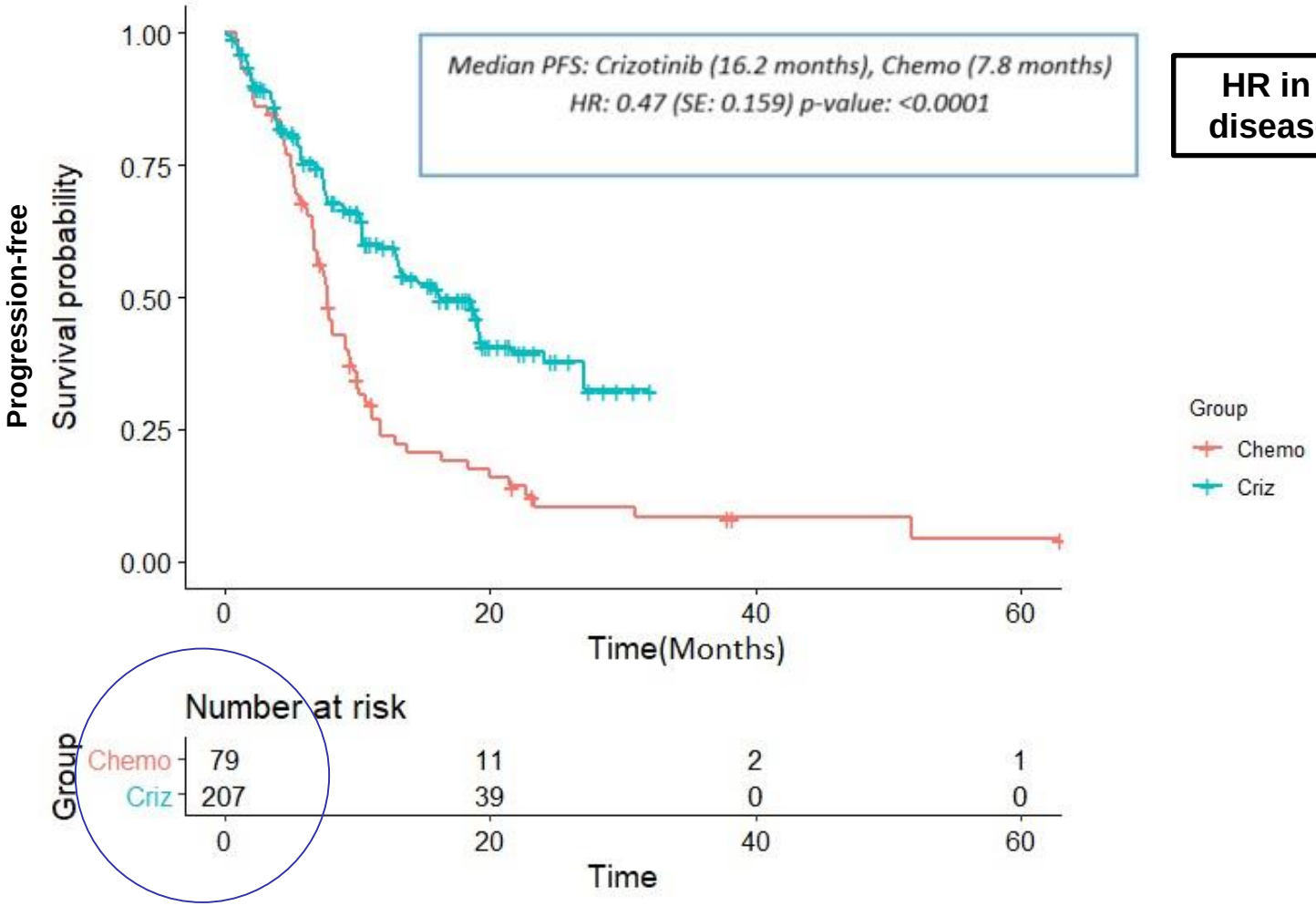
- ROS1-rearrangements found in ~1-2% of NSCLC cases
- Crizotinib, ALK+ targeted agent, activity against ROS1+ NSCLC
- No comparative trial evidence, small single arm studies
- Previous analyses relied on results in ALK+ population

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

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

Pooled survival analysis



HR in ALK+ disease: 0.48

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Cancer Care Ontario

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?

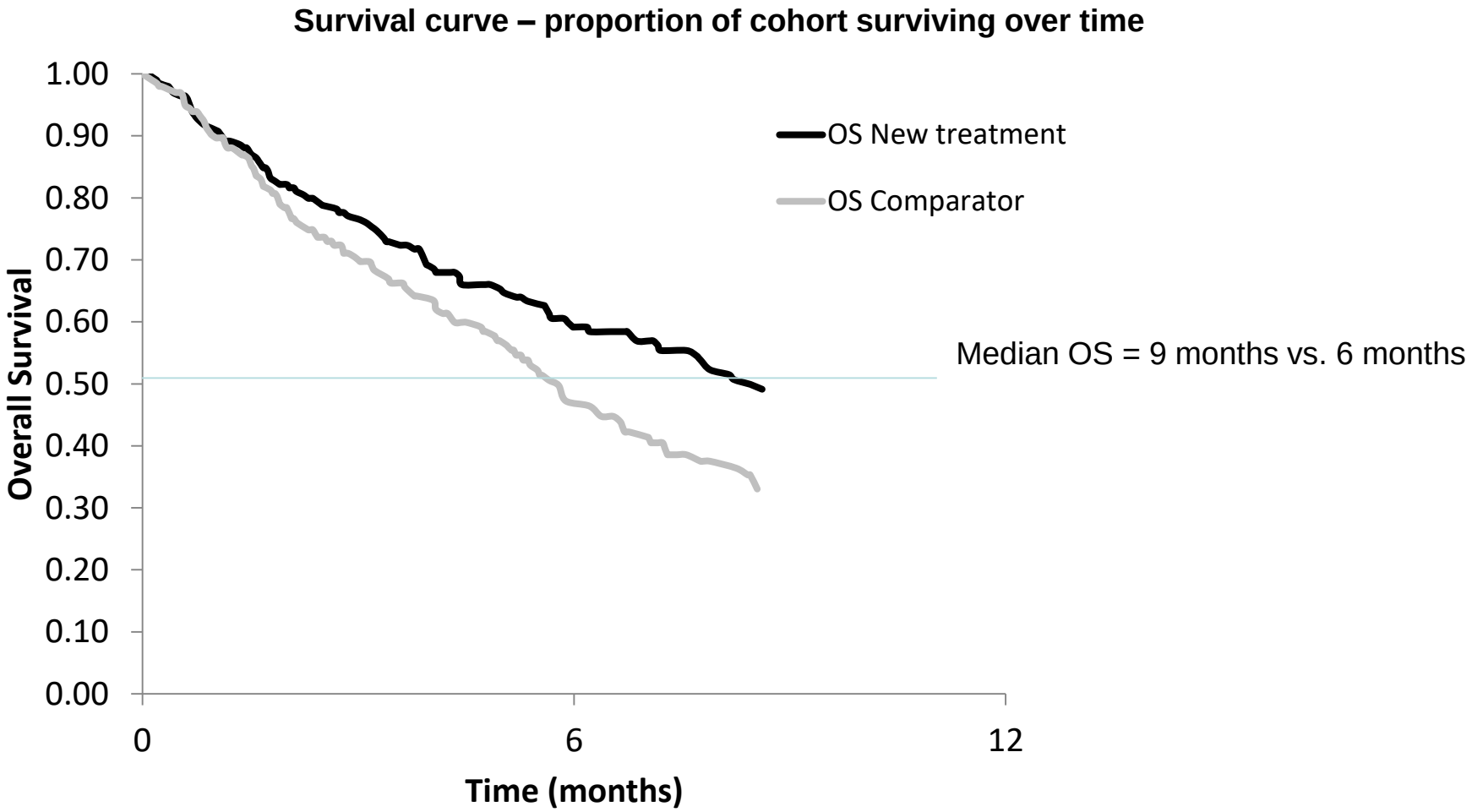
Pharmacoeconomics in cancer

- 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



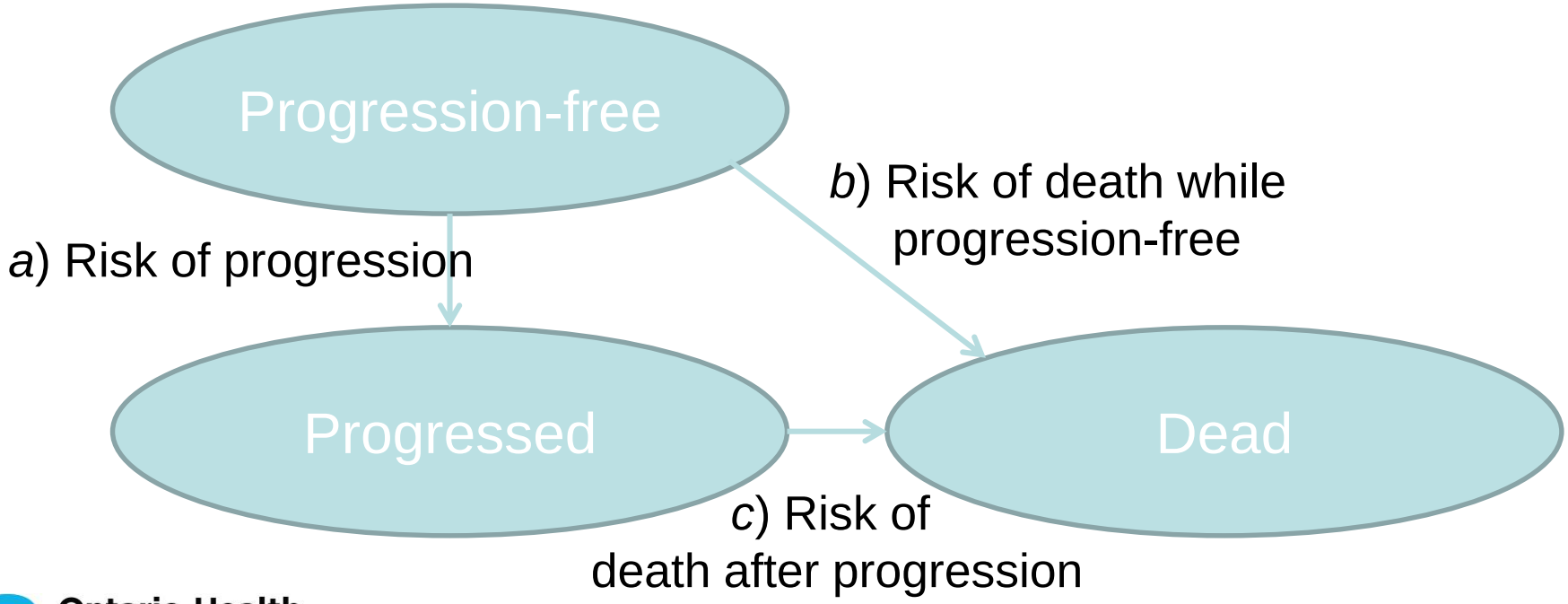
Two modelling approaches

- Estimate survival (life years):

Indirectly	Directly
Estimate risks of progressing from health states until reaching absorbing death state	Estimating (extrapolating) OS curves
Adding up time spent in the living health states	Adding up area-under-the-curve
Markov model	Partitioned survival analysis

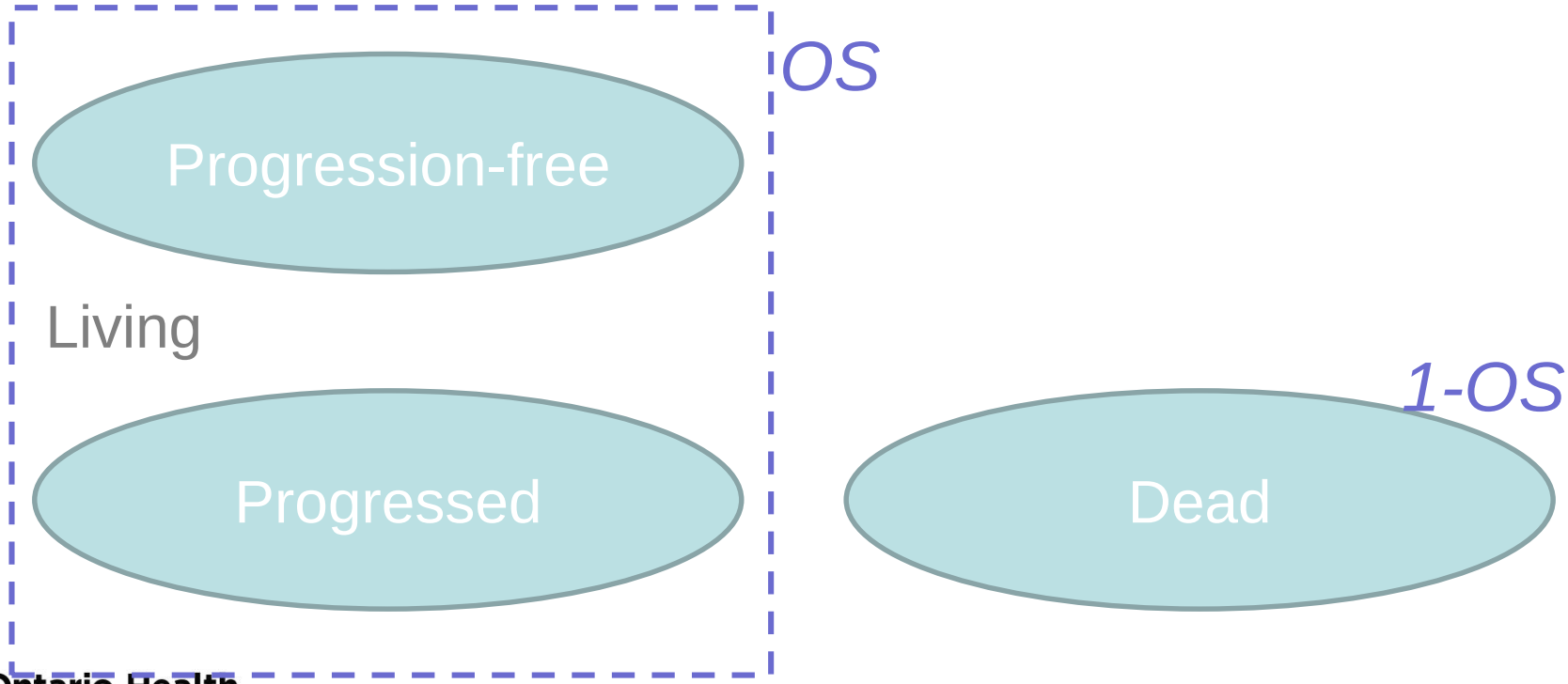
Markov model

- 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



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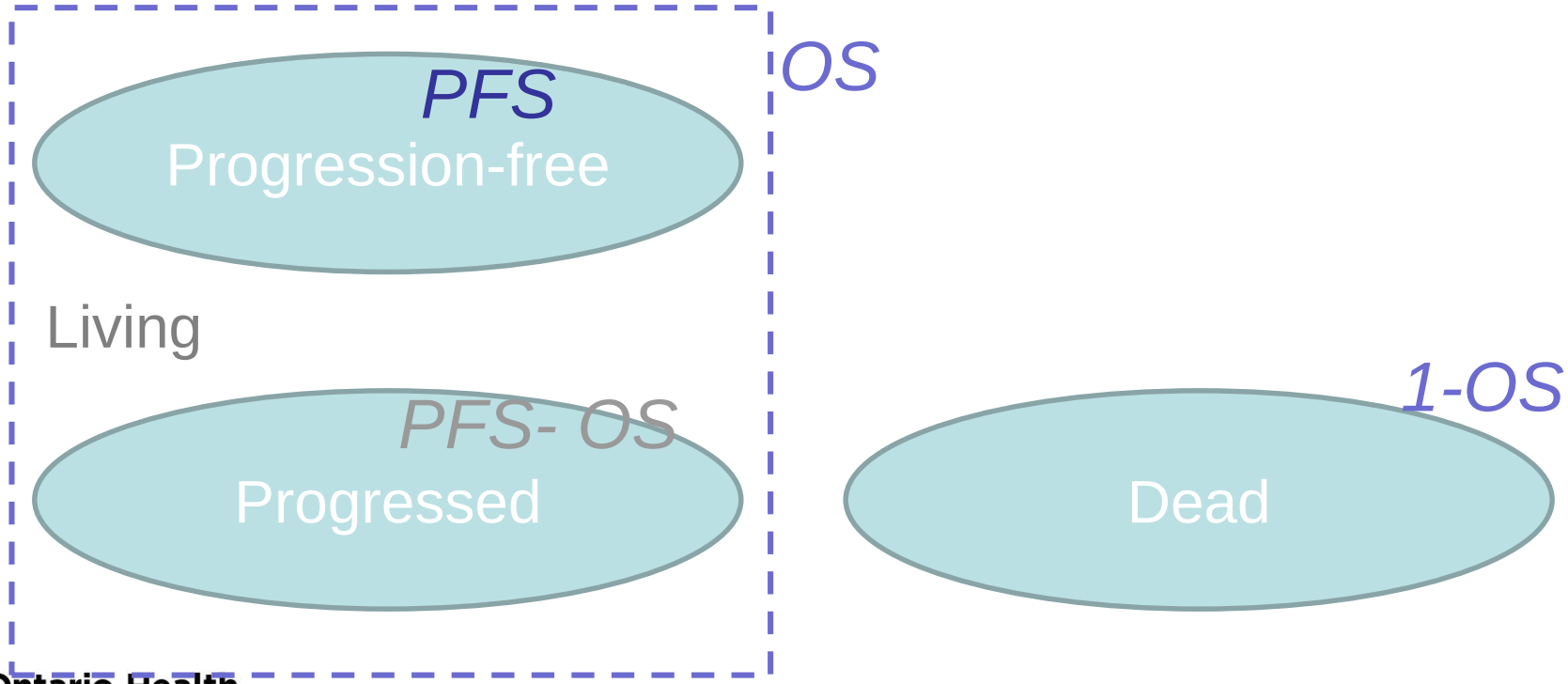
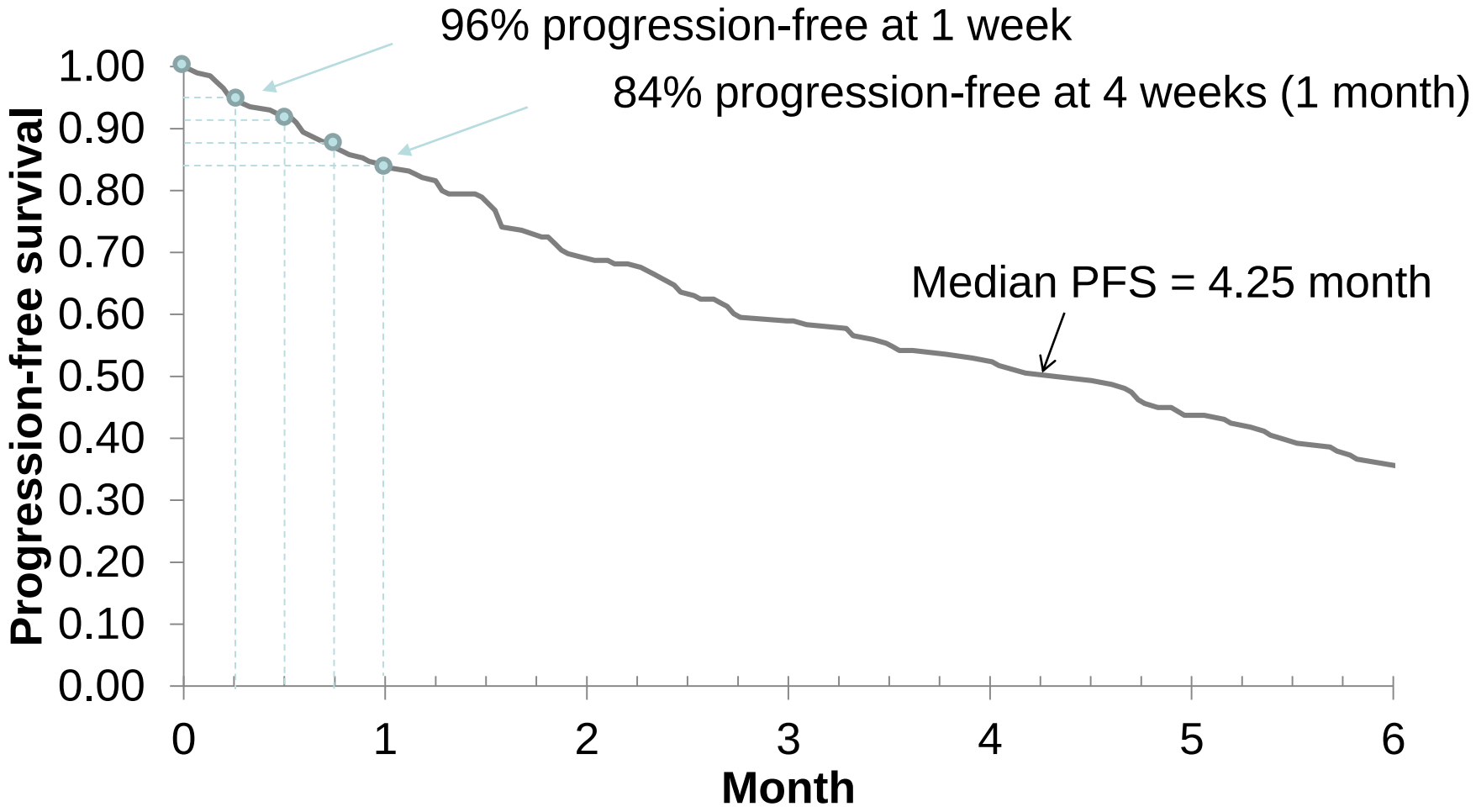


Estimating average survival
Proportion in health state over time



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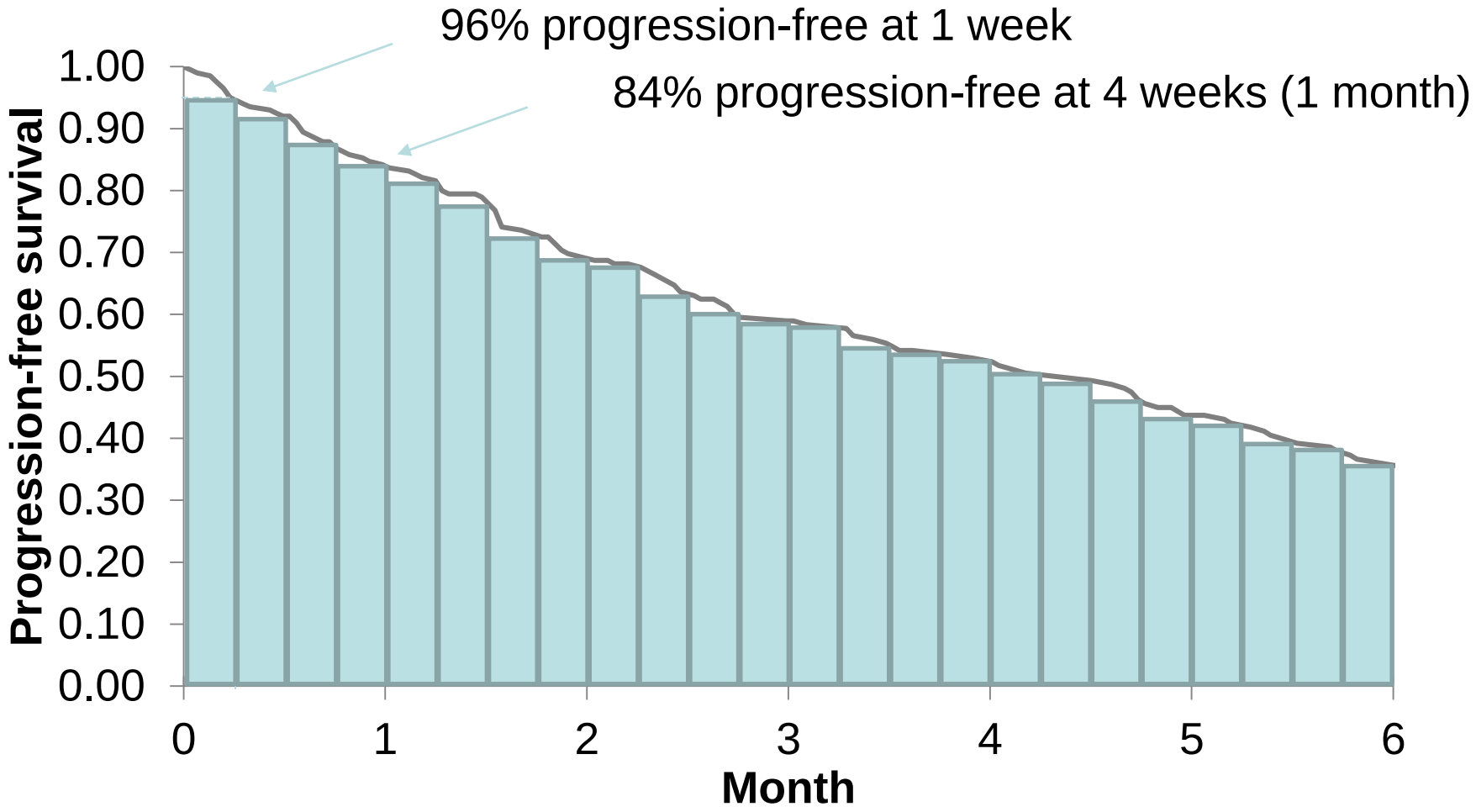
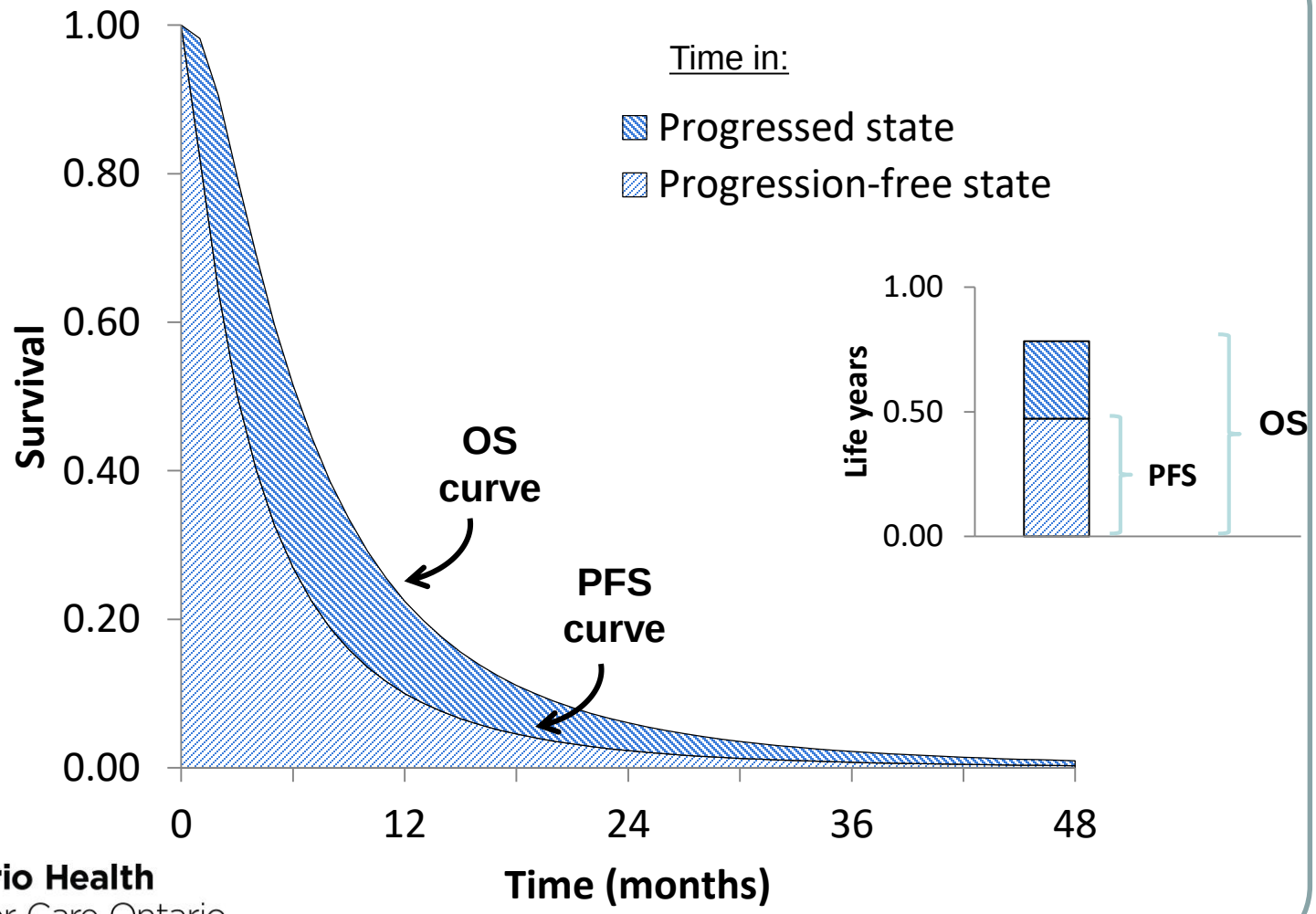
Estimating average survival
Proportion in health state over time

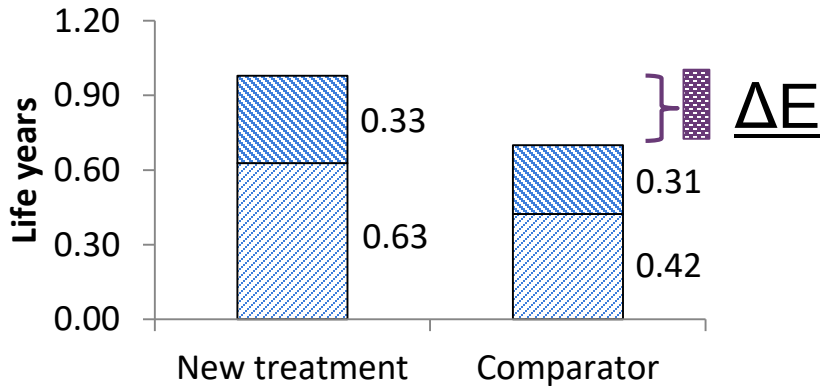


Partitioned survival models use areas under the curves to determine time in health states



Comparing two treatments

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

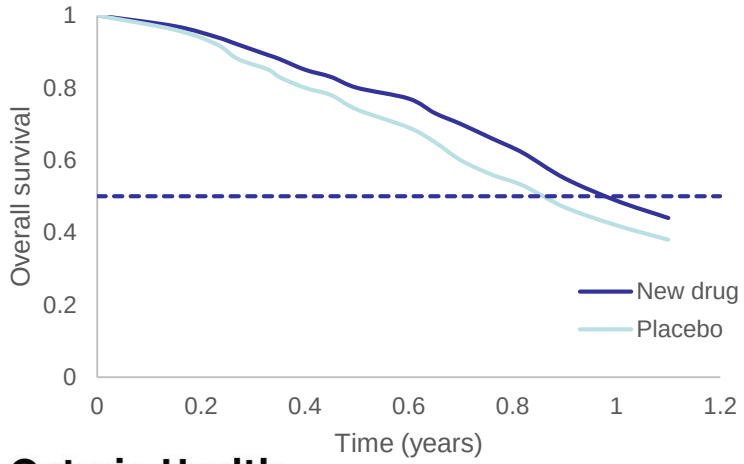


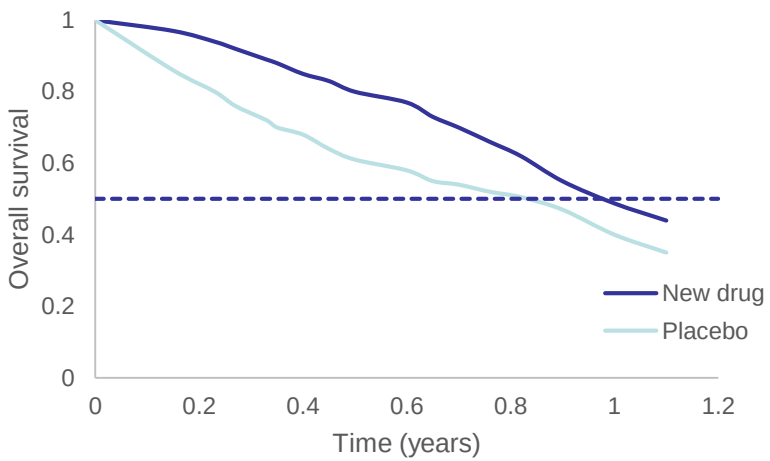
	Life years
New treatment	0.96
Comparator	0.73
Incremental (ΔE)	0.23

Pros and cons of partitioned survival models

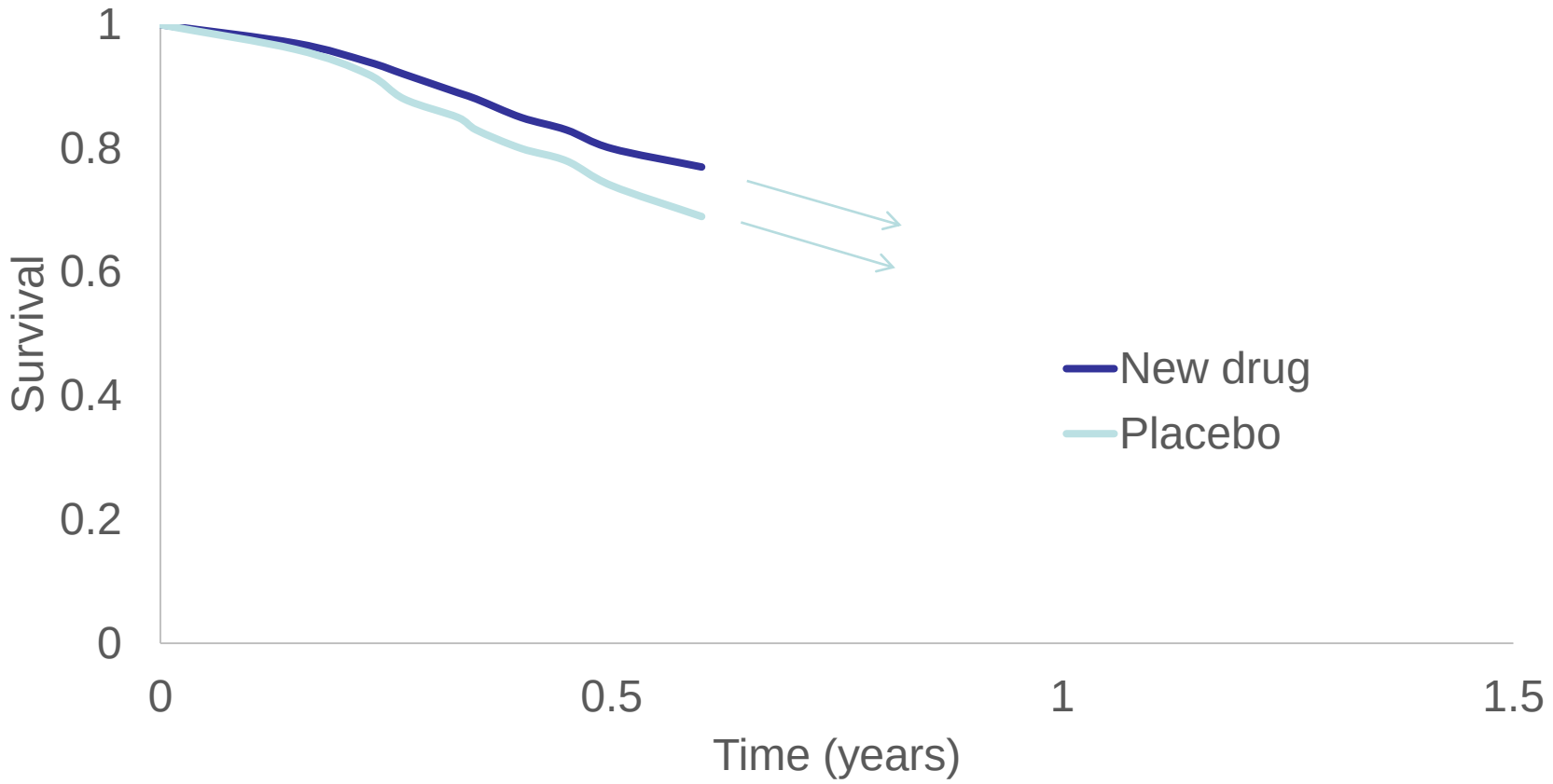
Pros

- 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



What does the guidance say?

CADTH METHODS AND GUIDELINES

Guidelines for the Economic Evaluation of Health Technologies: Canada

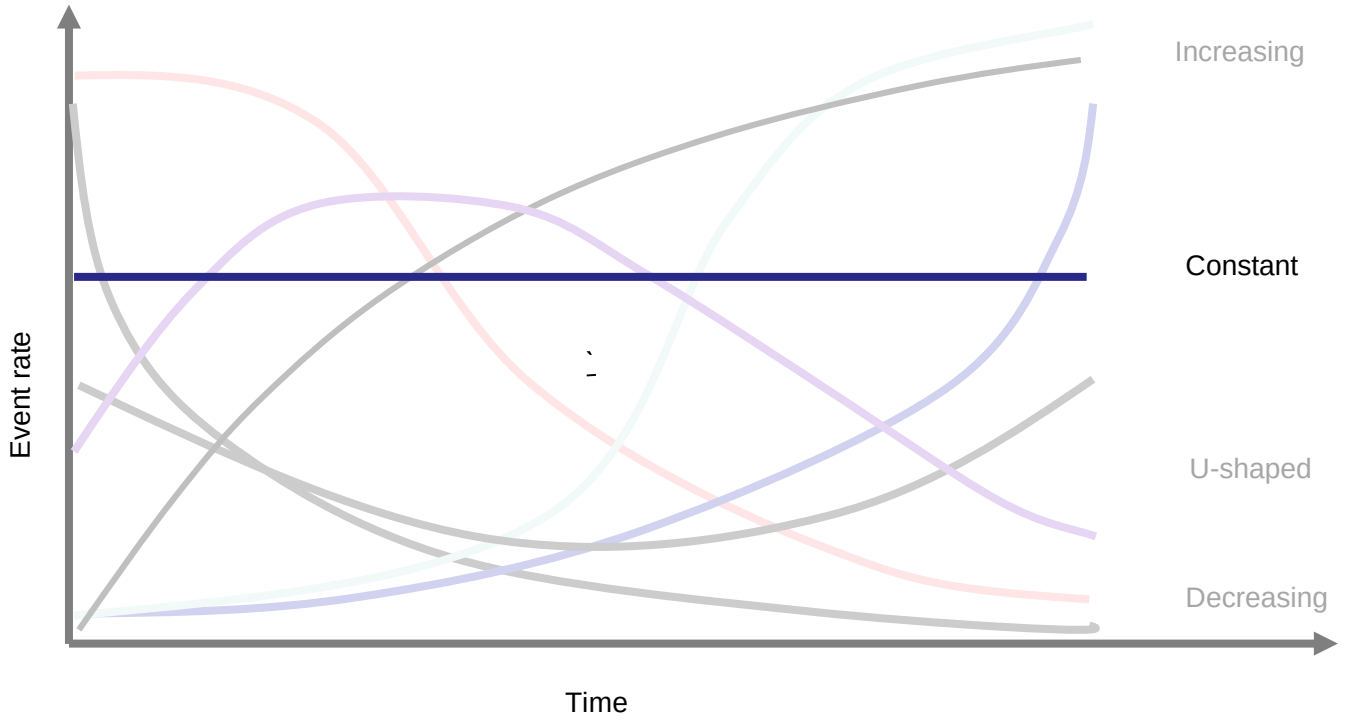
4th Edition

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.[67] 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).[68]

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



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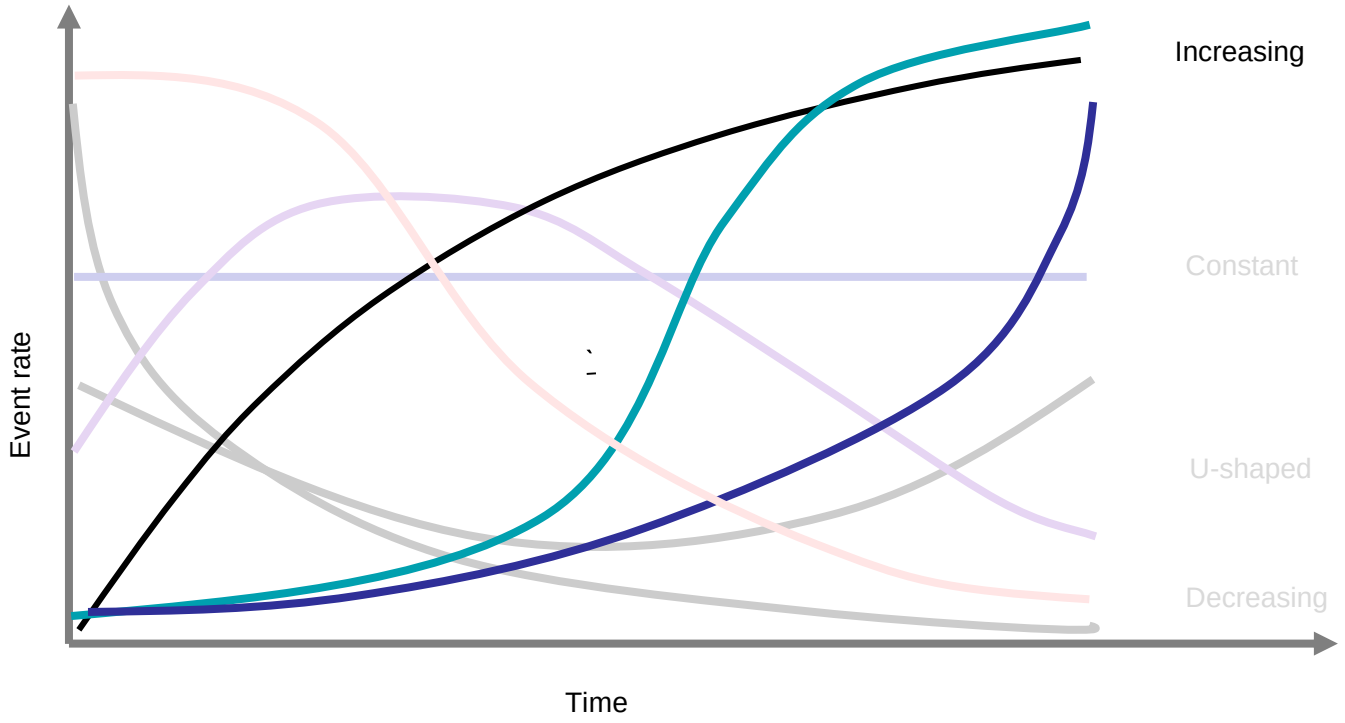

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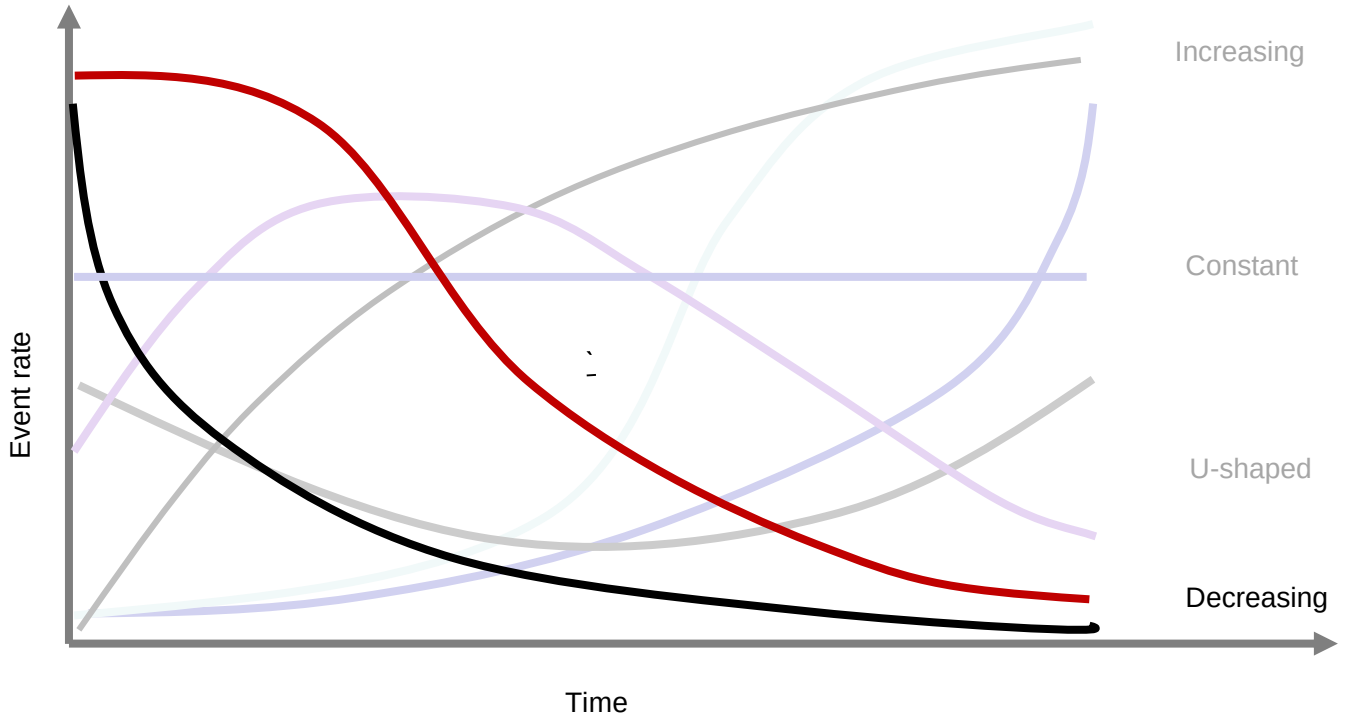

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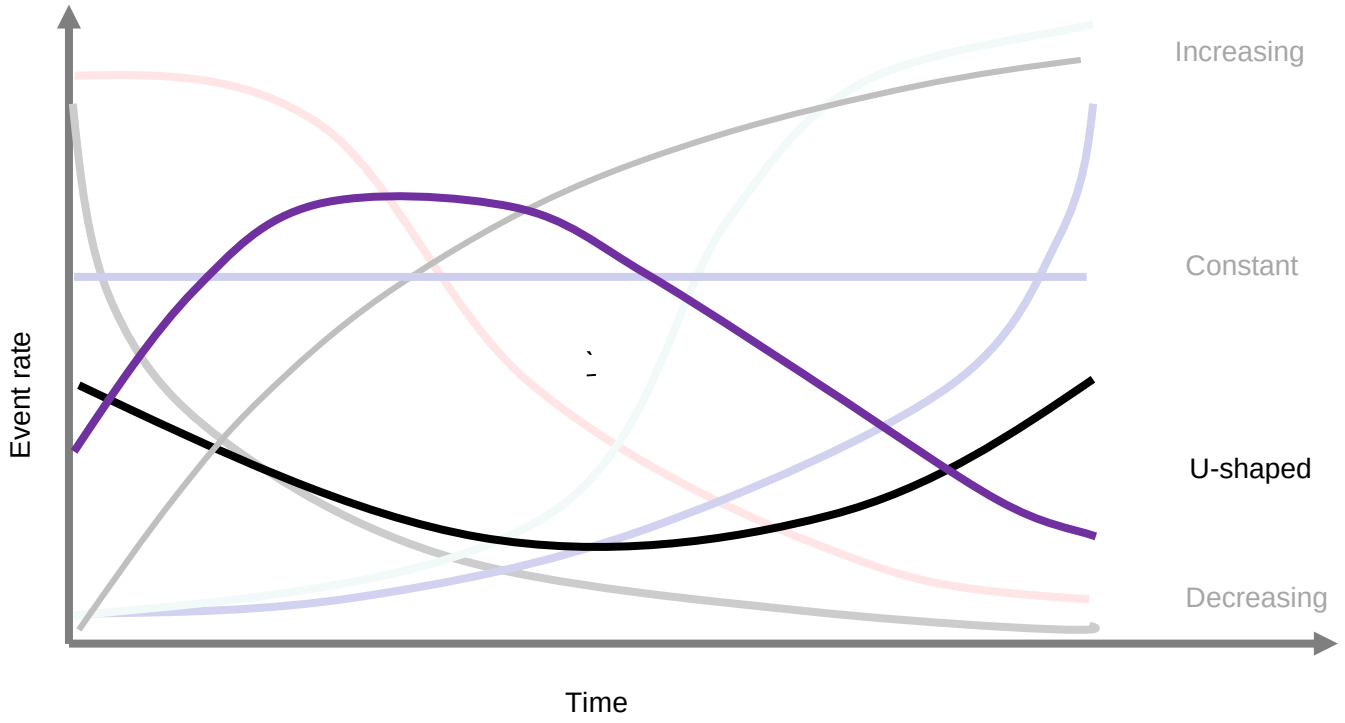

Some common parametric distributions

Table 1 Summary of key properties of commonly used parametric survival distributions

	Exponential	Weibull	Gompertz	Log-Logistic	Log-Normal
Risk pattern	Constant hazard	Monotonically increasing ($\gamma > 1$) or decreasing ($0 < \gamma < 1$) hazard	Monotonically increasing ($\gamma > 1$) or decreasing ($\gamma < 0$) hazard	Monotonically decreasing when $\gamma \leq 1$, or increasing followed by a gradually decreasing hazard when $\gamma > 1$	Log of the event time has a normal distribution
Type: PH vs. AFT	PH or AFT	PH or AFT	PH	PO or AFT	AFT
Survival function: $S(t) =$	$\exp(-\lambda t)$	$\exp(-\lambda t^{\gamma})$	$\exp\left[\frac{-\exp(\lambda)(\exp(\gamma t)-1)}{\gamma}\right]$	$\frac{1}{1+\lambda t^{\gamma}}$	$1-\phi\left(\frac{\log(t)-\lambda}{\gamma^{-1}}\right)$ where ϕ is the cumulative standard normal distribution

Choice related to: risk pattern (observed and beyond)

Ishak et al 2013

Different assumptions can produce very different estimates

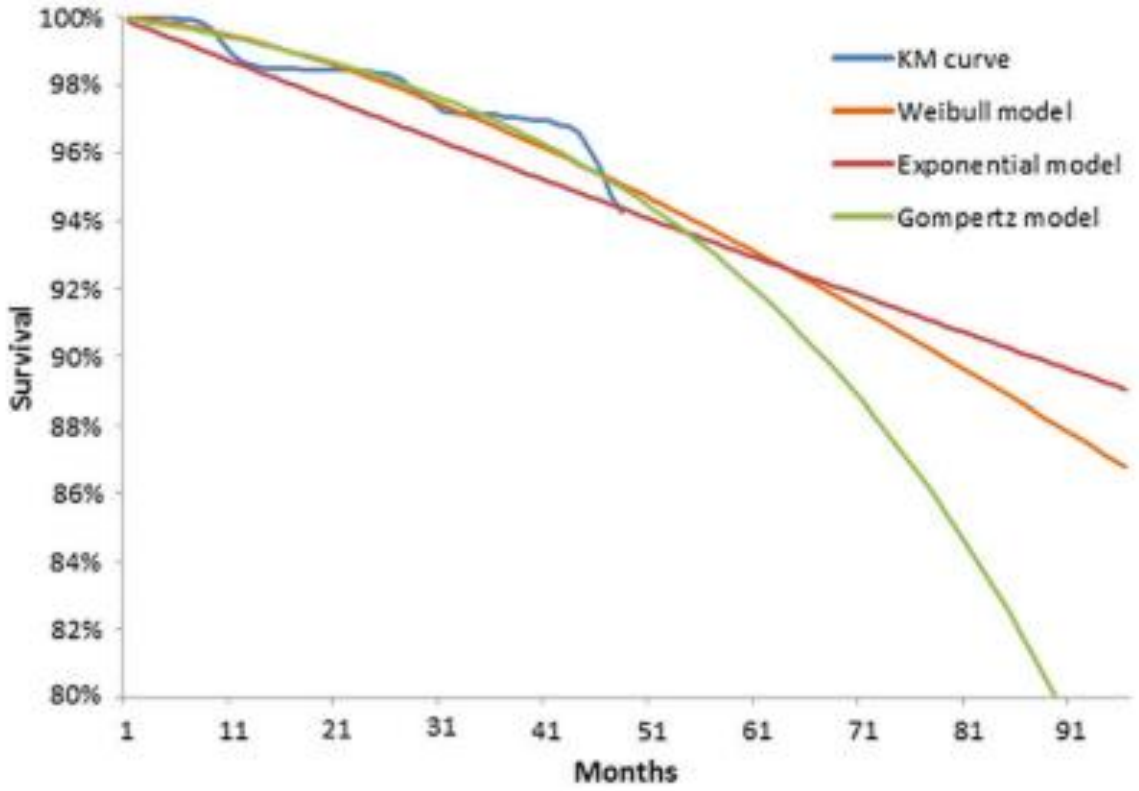

Fig. 2 Illustrative survival data from a hypothetical clinical trial fitted using different parametric models

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Francois et al (2019) https://doi.org/10.1007/978-3-030-01207-6_3

NICE DSU TECHNICAL SUPPORT DOCUMENT 14: SURVIVAL ANALYSIS FOR ECONOMIC EVALUATIONS ALONGSIDE CLINICAL TRIALS - EXTRAPOLATION WITH PATIENT-LEVEL DATA

REPORT BY THE DECISION SUPPORT UNIT

June 2011

(last updated March 2013)

Incomplete survival data:

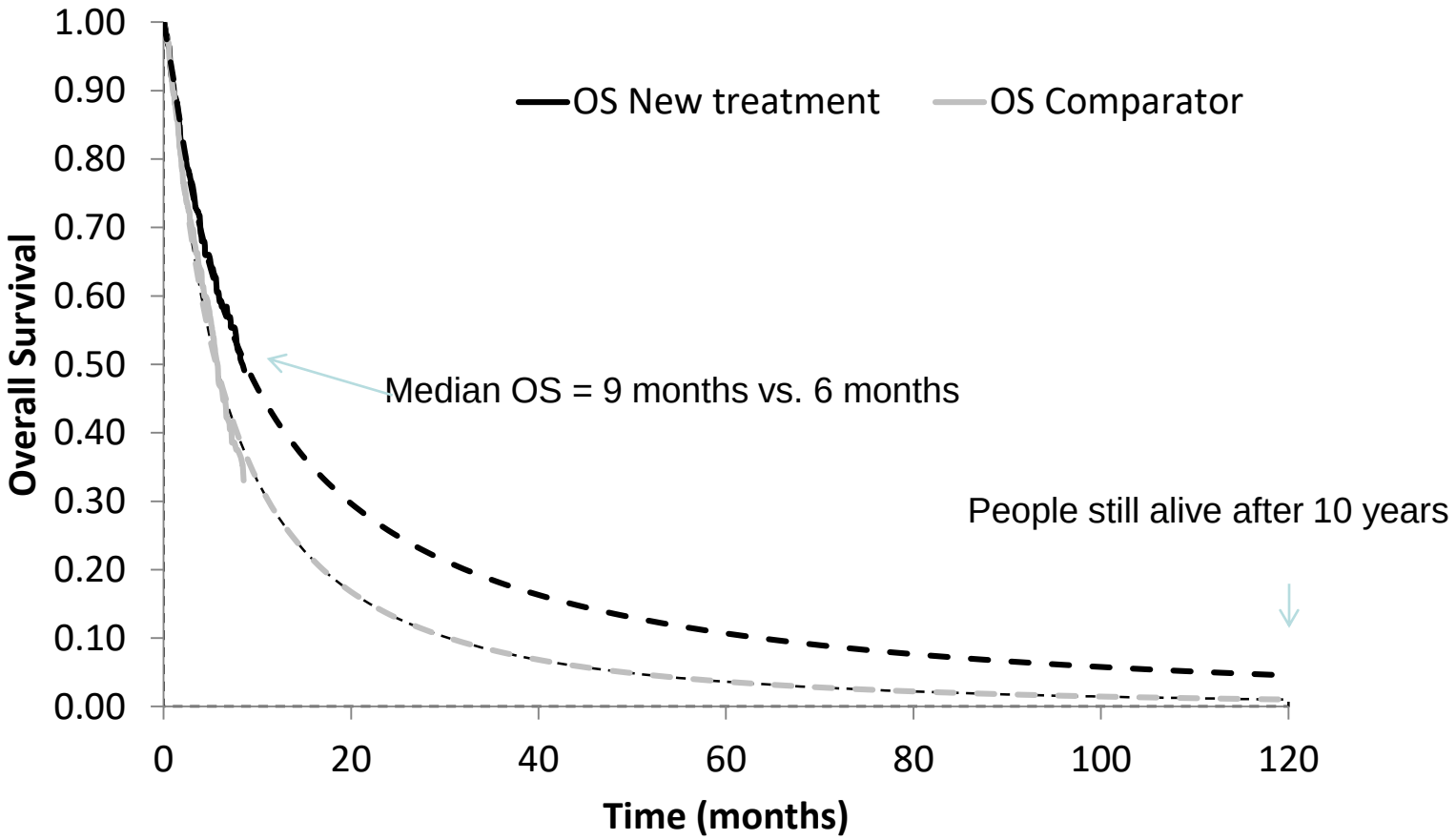
- Visual inspection
- External data
- Clinical validity
- AIC
- BIC
- Log-cumulative hazard plots
- Other suitable tests of internal and external validity
- Consider duration of treatment effect

Nicholas Latimer

degree of censoring present. If very little extrapolation is required and there is little censoring, the fit to the observed data is of most importance. However, if substantial extrapolation is required, the plausibility of the extrapolated portion of alternative models is of greater importance than the fit to the observed data.

Need for estimates to be 'plausible' long-term – But no formal guidance for how to evaluate

Problem when extrapolation produces unrealistic survival benefits



Pros and cons of partitioned survival models

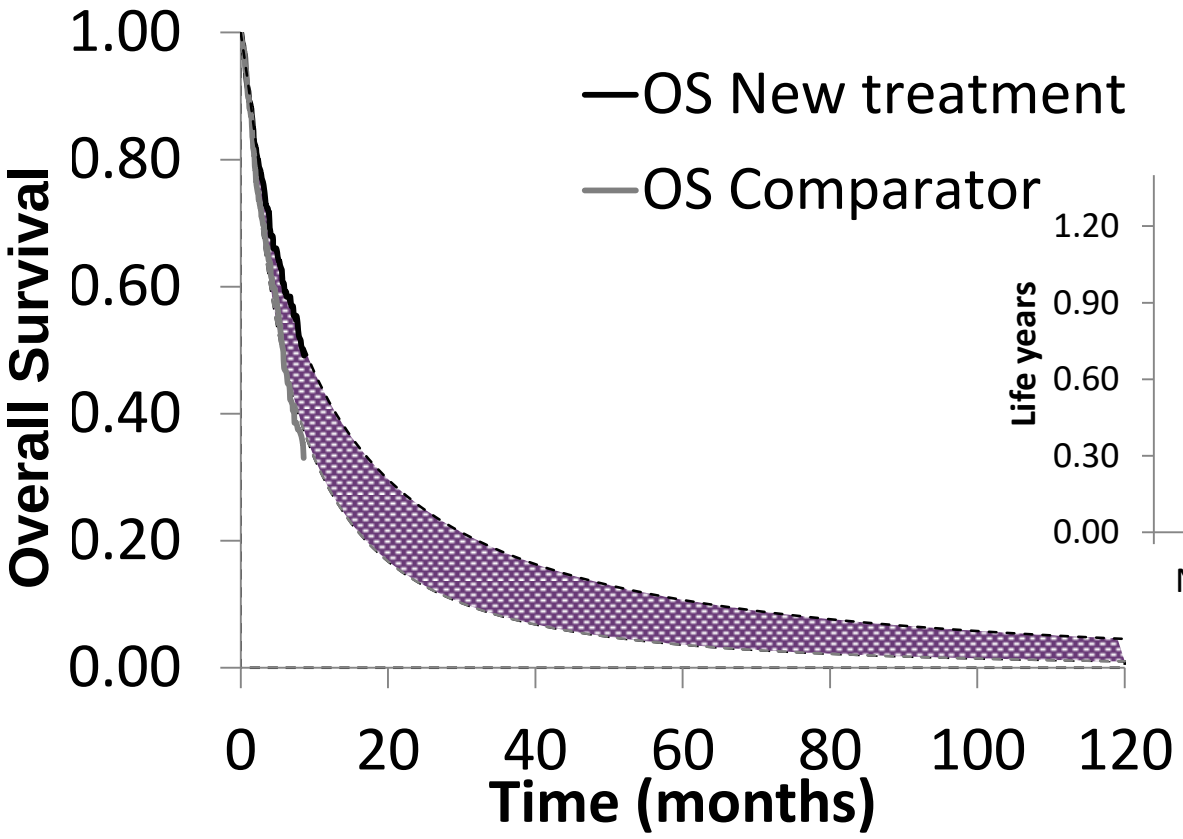
Pros

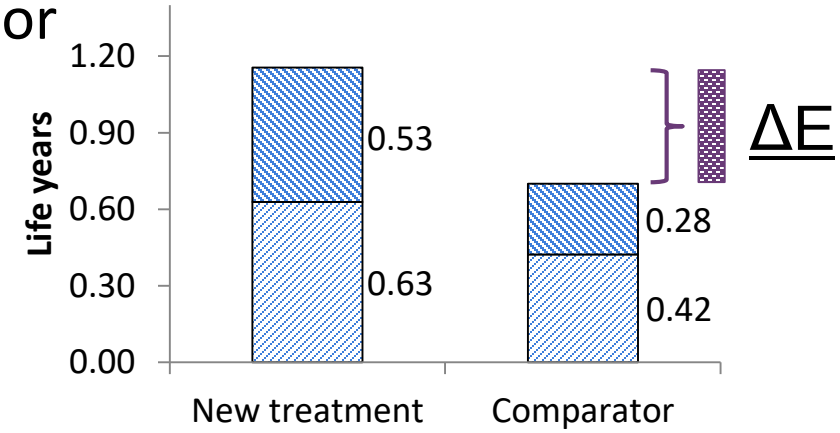
- Aligns with trial outcomes (PFS, OS data used directly)
- Recreates observed data well
- Closely capture small differences in survival, reflect incremental gains

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

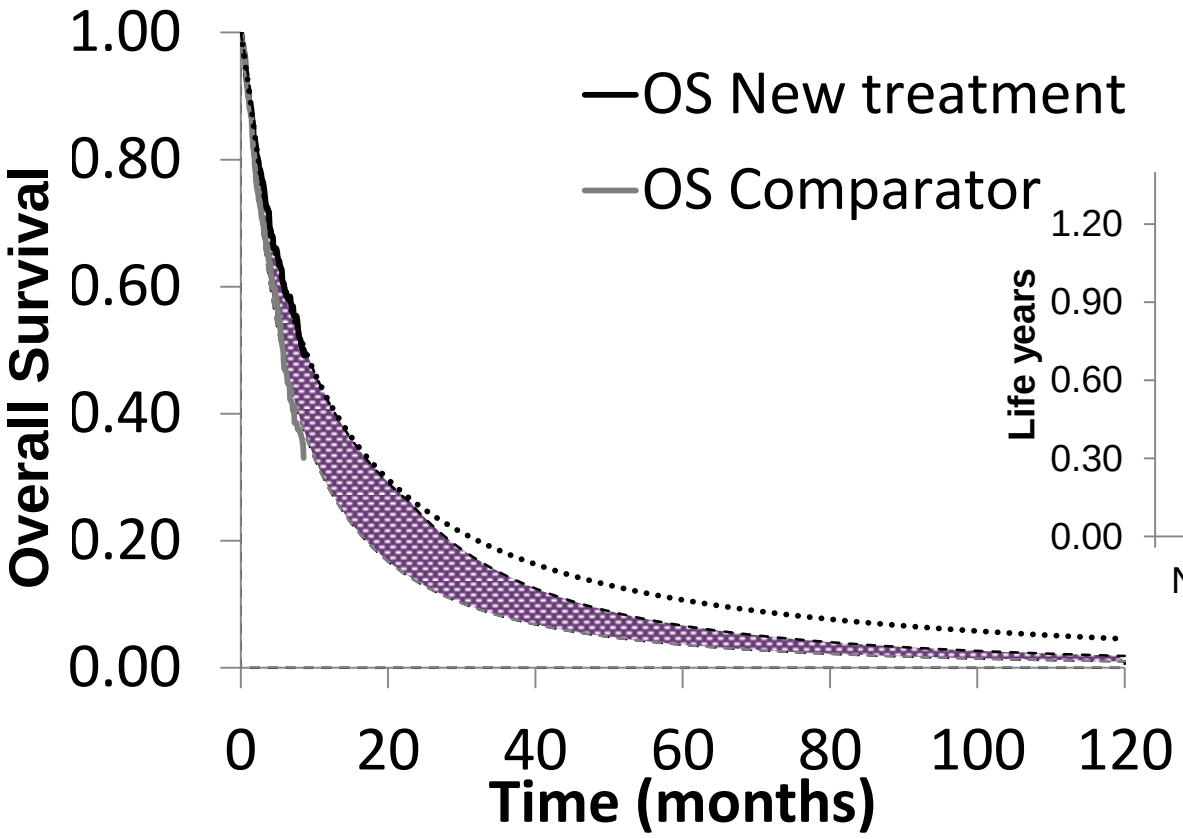
Problem when model produces implausible added benefits after progression

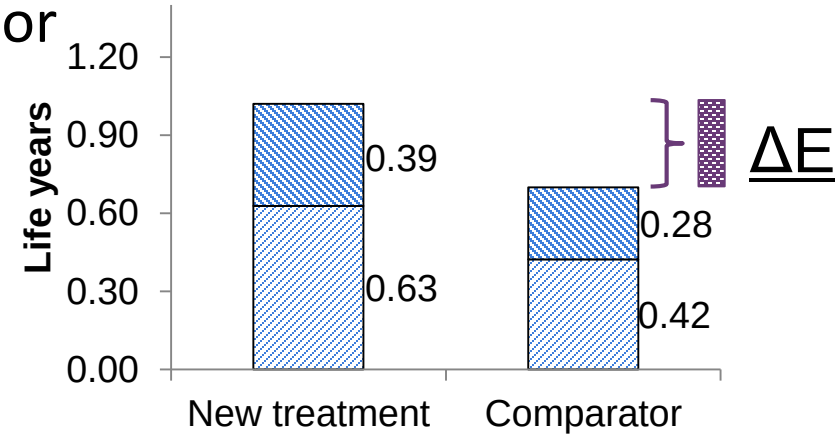




At some point, risk pattern might change
Treatment unlikely to reduce risk indefinitely

Could assume HR=1





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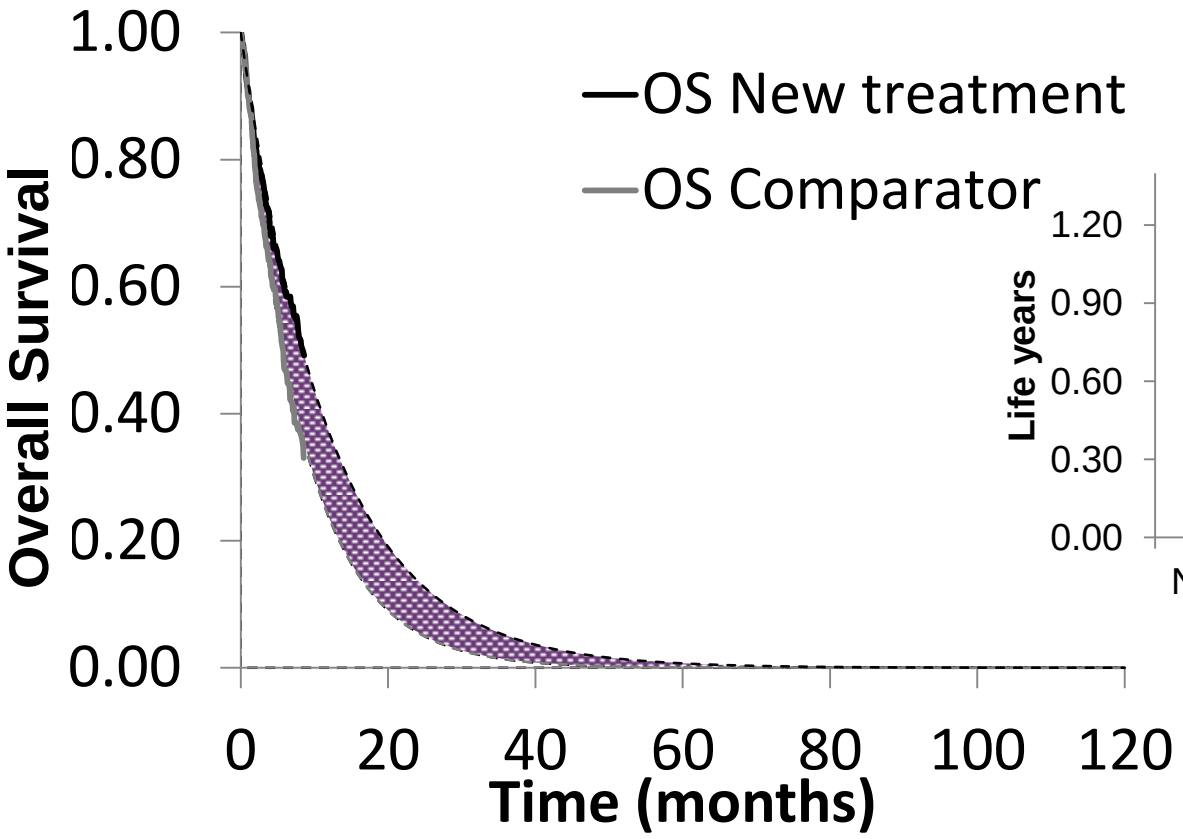
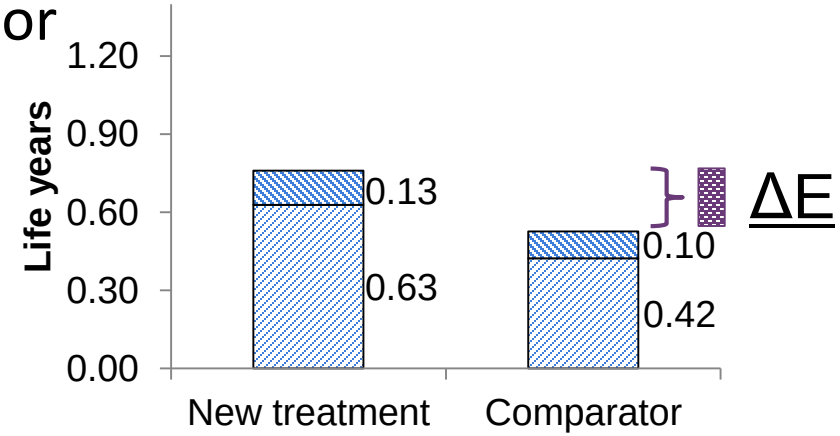
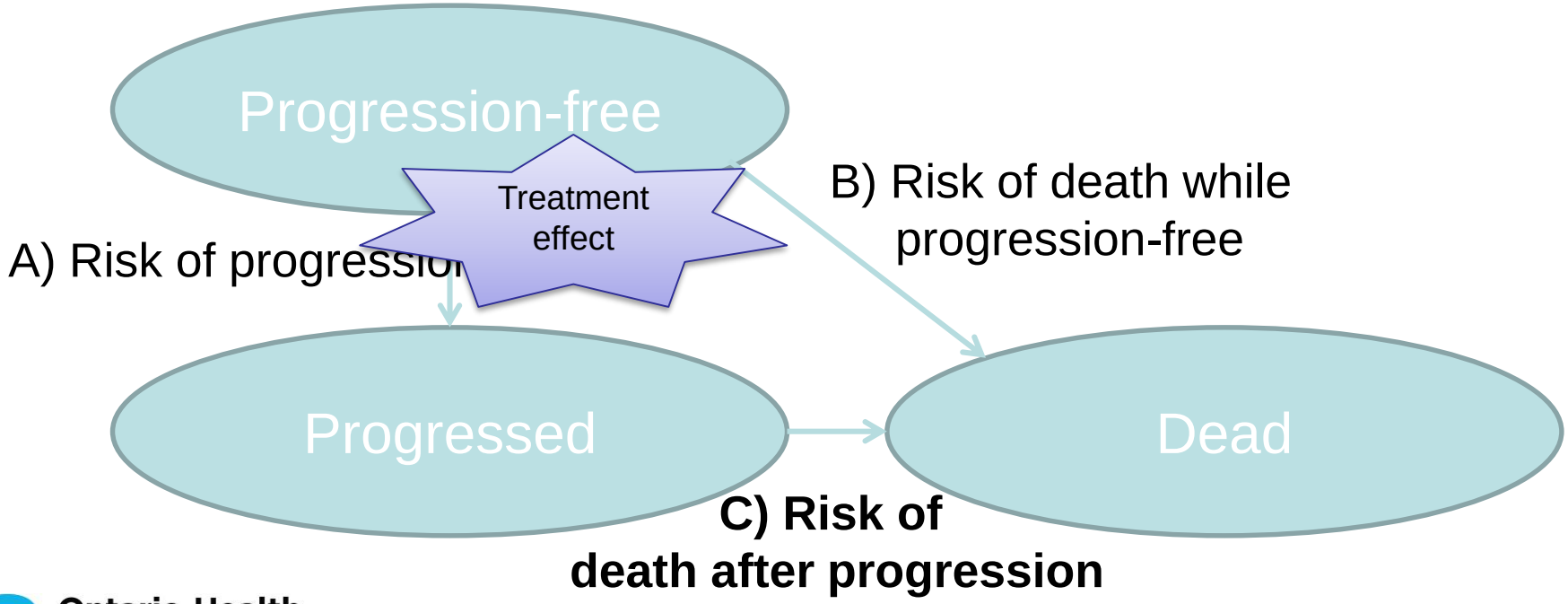
Other distributions may be more plausible long term – Structural uncertainty from choice





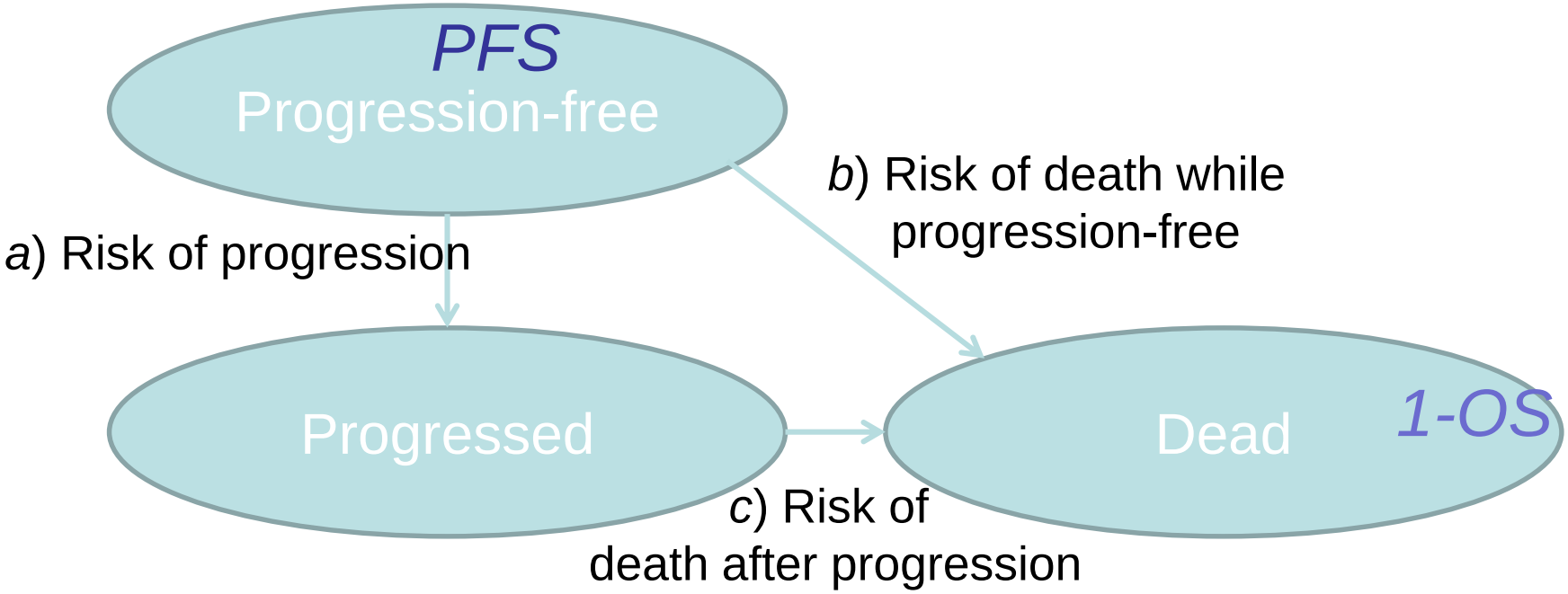
Benefits of Markov models

- 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



So what's the difference?

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



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 Woods[1], Eleftherios Sideris[1], Stephen Palmer[1], Nick Latimer[2], Marta Soares[1]

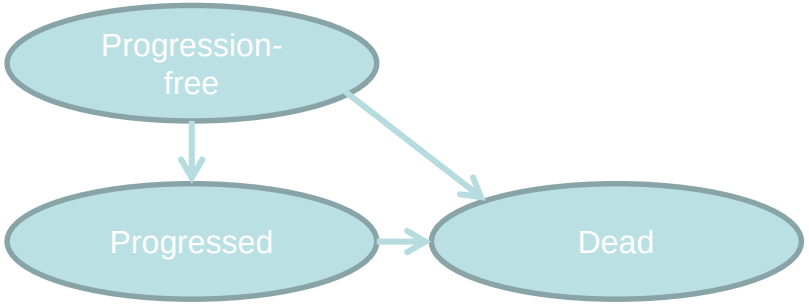
PharmacoEconomics
DOI 10.1007/s40273-017-0583-4

CURRENT OPINION

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

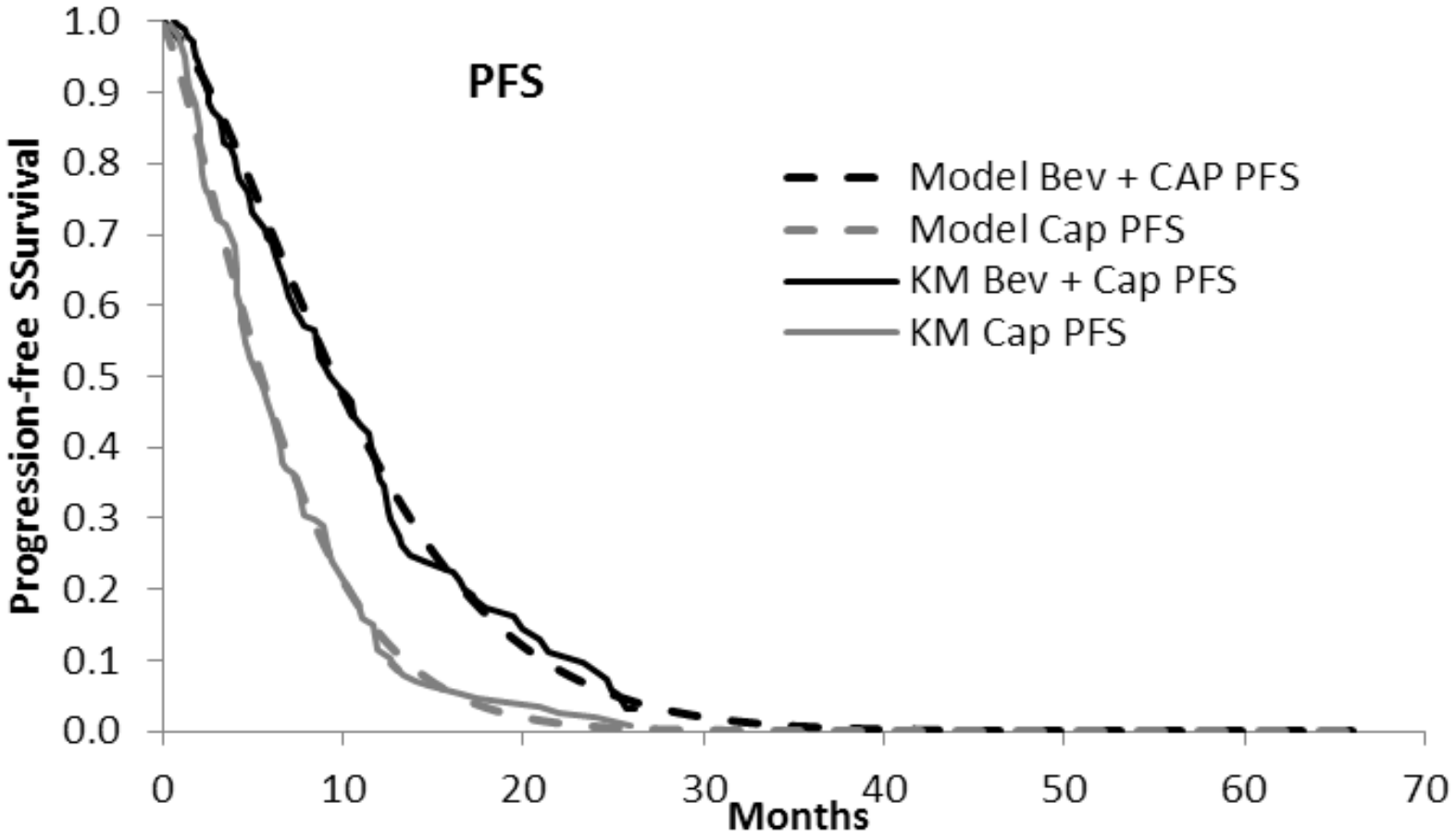
Jaclyn Beca[1] · Don Husereau[2,3] · Kelvin K. W. Chan[4,5] · Neil Hawkins[6] · Jeffrey S. Hoch[7]

Case study



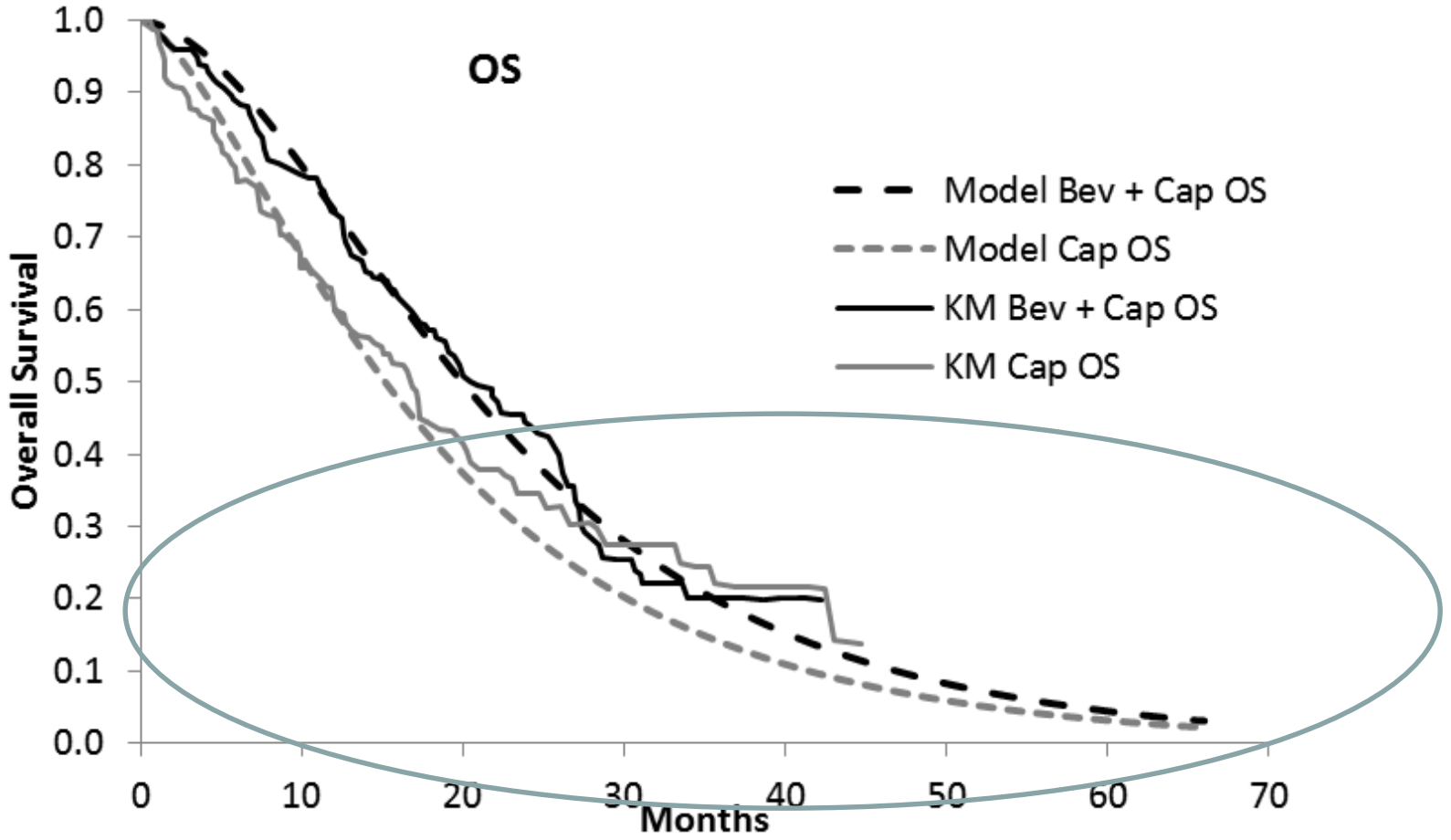
- Bevacizumab + capecitabine (new strategy) vs. capecitabine alone (comparator) for first line metastatic colorectal cancer
- Developed 3 state partitioned survival and 3 (also 4 and 5) state Markov model
- Fit parametric distributions to recreated trial survival data (AVEX)
  - PFS for both models and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

Survival curve fitting - PFS



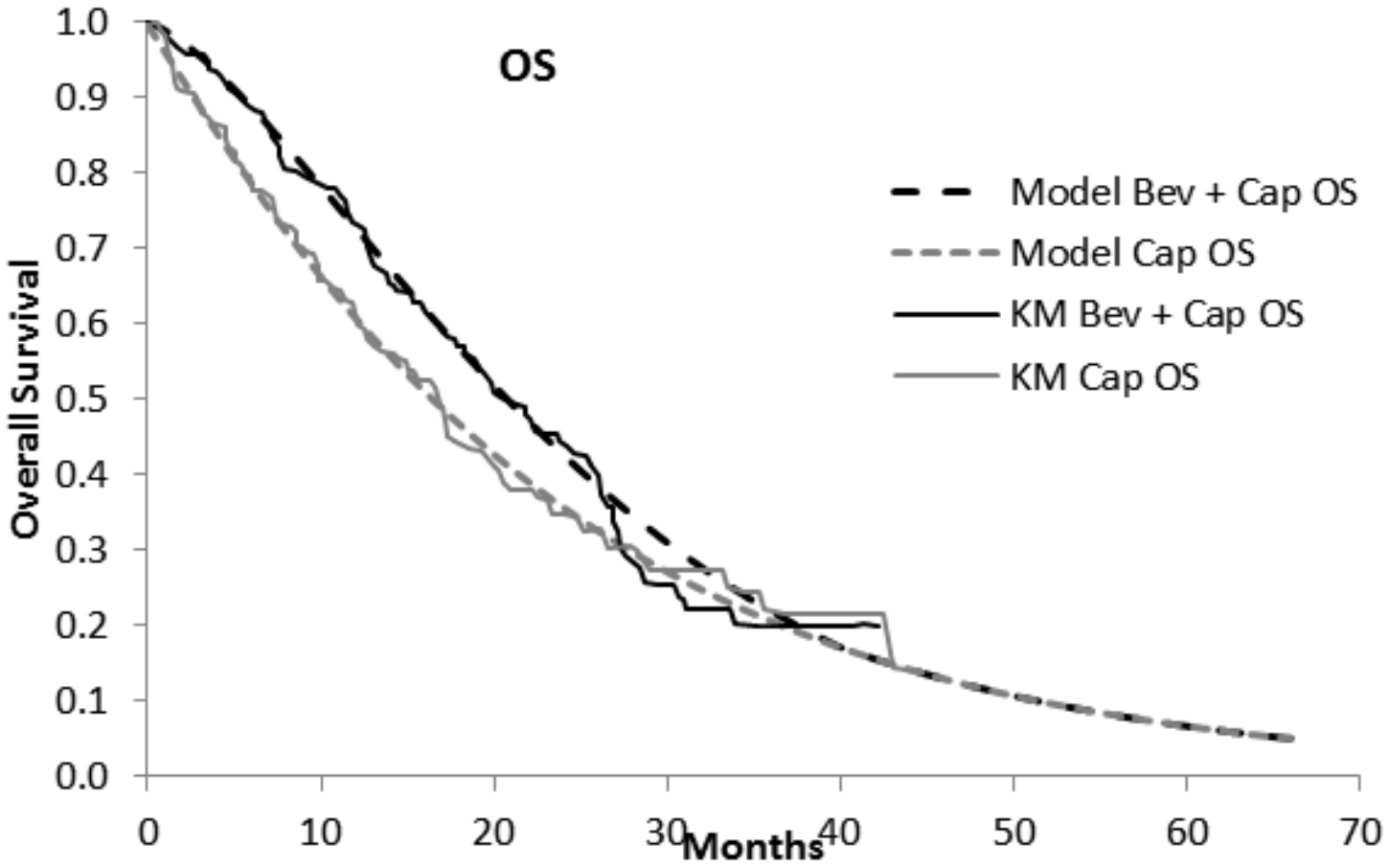
KM data digitized using Engauge software from Cunningham et al 2013

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

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

- 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

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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