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The PBS and drug reimbursement- Perspectives on Novel Medicines?

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Menzies Centre for Health Policy

Access to Novel Medicines

- Context of Medicines Funding in Australia
- How do medicines get considered by the PBAC
- Current Issues and Challenges for Funding Novel Drugs in Australia

Medicines
It's an Exciting Time

- New drugs and therapies.
  - More effective drugs in new classes
  - Drugs where no previous pharmaceutical option
  - CAR-T and other gene therapies
- New approaches.
  - Many drugs need to be taken for indefinite period or for indefinite number of cycles
  - Better biomarker targeting
  - Pan-biomarker therapies
- A changing industry.
- Growing community expectations.

PBS – the basics

- Main but not not only federal Government subsidy program for medicines
- In operation for over 60 years
- Over 900 different medicines & 5455 brands/products
- Over 205 million scripts in 2018-19 with PBS expenditure of over $11.8B
- Since 1993 Cost-effectiveness assessment mandatory
- Increasing proportion spent on high cost drugs especially cancer and immunomodulating drugs

Choosing drugs for subsidy

- Prerequisite: registered drug (TGA)
  - Assesses efficacy, safety, quality
- Pharmaceutical Benefits Advisory Committee (PBAC) "recommends"
  - Assesses **comparative** effectiveness, **comparative** safety, **comparative** costs
- Minister "declares"
  - Accepts/rejects recommendation
  - Government provides the funding

Context of PBAC Decision making

- Established under the *National Health Act 1953*.
- Recommends to the Minister for Health which medicines should be subsidised under the PBS.
- Required, under the Act, to consider the effectiveness and cost of the proposed medicine compared with existing (alternative) therapies (s101).
- It cannot make a positive recommendation for a medicine that is *substantially more costly than an alternative medicine unless it is satisfied that the proposed medicine also provides a significant improvement in health* for at least some people.

PBAC Outcomes

- Recommend
  - Cost-minimisation (no price advantage)
  - Acceptable cost-effectiveness (price advantage)
- Reject
  - Incremental cost-effectiveness ratio unacceptably large
  - High level of uncertainty – quality of evidence
  - Concerns about total cost
  - Concerns about usage beyond restriction
- Deferral
  - Other information requested by the PBAC
  - Not yet registered with the TGA
- This information is made publicly available on the PBS website – Public Summary Document

Quantifiable factors influencing PBAC decision making

- Comparative health gain
- Comparative cost-effectiveness
- Patient affordability in the absence of PBS subsidy
- Predicted use in practice and financial implications for the PBS
- Financial implications for the Australian Government health budget

Less Quantifiable factors influencing PBAC decision making

- Overall confidence in the evidence and assumptions relied on in the submission.
- Equity.
- Presence of effective alternatives.
- Severity of the medical condition treated.
- Ability to target therapy with the proposed medicine precisely and effectively to patients likely to benefit most.
- Other public health considerations
  - Eg prudent use of antibiotics, QUM

Some Reasons PBAC Decision Making is Harder

- Less certainty about comparative effectiveness and harms
- Value of Incremental Gains
- Community expectations of earlier access
- Rare and Rarer diseases
- Higher price expectations
- Pharma changes

A Challenge:

- How to make new drugs/therapies available to Patients/Clinicians faster without compromising safety and value for public funding.

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When is Medicine Novel?

Novel

- First in new therapeutic class for disease/condition with existing PBS listed treatments
- Medicine for disease/condition where no previous drug therapy existed

New Medicine

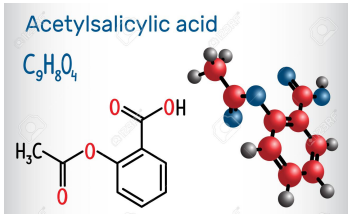
- New drug in existing listed class of medicines
- Novel combinations of existing listed medicines

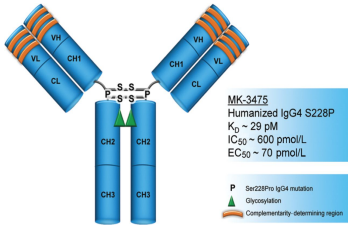
Accessory Medicine

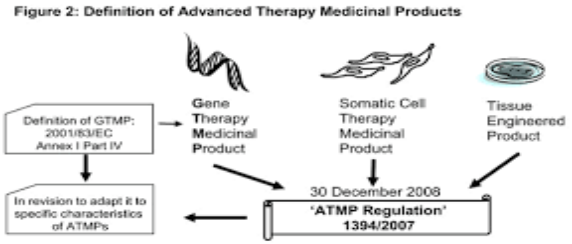
- Generics, biosimilars

?Repurposed and Repositioned Medicines?

Evolution of the Concept of "Drug"







Chemicals → Biologicals → Advanced Therapy Medicinal Products (ATMPs)

Reproducibility of Product - Predictability of action -
Product Quality - Evidentiary Standards (CMC, GLP, Clinical)

Increasing Complexity

The Onslaught has Just the Start!

- Currently 14 Advanced Therapeutic Medical Products authorized on EU market (out of 22 submitted and reviewed as of August 2019)
- Probably 1000 ATMP clinical trials underway globally, with about 100 in advanced (Phase III equivalent) trials
- Further 12 ATMPs likely to be approved in next 18 months (EU and US)
- Longer term estimated 25% of all new approved drugs will be ATMPs

Major Issues in Assessing Value of New Drugs

- Quality and quantity of evidence of effectiveness and harm particularly with pressure to bring to market earlier.
- Place in therapy especially for new therapeutic approaches rather new generation within class.
- Targeting of therapy – molecular markers
- Price expectations and global price setting.
- Cost of incremental increases.
- Patient and clinician inputs.

Process Changes relevant to Novel Medicines

- Parallel submissions TGA/PBAC already reduced time to HTA decision (most new medicines)

- Just commenced - Facilitated pathway post initial PBAC consideration for novel medicines with potentially high therapeutic value.

- Recommendations categorized to support accelerated post PBAC processes to listing for medicines of high added therapeutic value.

Govt Accepted TGA Response to Review

- Priority Review –
  - same standard, faster assessment of prescription medicines with a full data dossier in certain circumstances.
- Provisional Approval
  - Different standard, earlier access to certain promising new medicines that do not yet have a full dossier of clinical data.
  - time limited registration pending evidence
- Enhanced medicines vigilance
  - strengthen post registration monitoring of medicines (and devices).

Eligibility Criteria: Provisional Determination

1. Medicine	**a new indications medicine OR a new prescription medicine**
2. Serious condition	an indication of the medicine is the treatment, prevention or diagnosis of a life threatening or seriously debilitating condition AND
3. Comparison against existing therapeutic goods	either: i. no therapeutic goods that are intended to treat, prevent or diagnose the condition are included in the Register (except in the part of the Register for provisionally registered goods) OR i. if one or more therapeutic goods that are intended to treat, prevent or diagnose the condition are included in the Register (except in the part of the Register for goods known as provisionally registered goods)—there is preliminary clinical data demonstrating that the medicine is likely to provide a significant improvement in the efficacy or safety of the treatment, prevention or diagnosis of the condition compared to those goods AND
4. Major therapeutic advance	there is preliminary clinical data demonstrating that the medicine is likely to provide a major therapeutic advance AND
5. Clinical study plan	the person who made the application under subsection 22C(1) of the Act has provided sufficient evidence of the plan to submit comprehensive clinical data on the safety and efficacy of the medicine before the end of the 6 years (starting on the day that provisional registration of the medicine would commence if the Secretary were to provisionally register the medicine).

PD - Issues and Options for PBAC

- Issues
  - High uncertainty on need, effectiveness and safety
  - Very high uncertainty on modeled cost-effectiveness
  - Limited real world experience to determine likely positioning and patient populations
  - 6 year window for new data – most new medicines will have recovered costs and have competitors – experience elsewhere variable on completion of such requirements
- Options
  - Pricing that reflects uncertainty
  - Managed (early) access program
  - Treat as what it really is – public funding to share risk of development

Relevant Questions for Managed Access Programs

- Benefits and safety in practice
- Review of optimal practice/utilisation
- Refinement of patient selection criteria
- Adjustment of limits around frequency/interval for use
- Adherence to stepwise diagnostic/treatment pathways
- Changing who renders a service (limiting or broadening prescribing rights)
- Narrowing where a technology can be used (CAR-T)
- Enforcement of technology as a replacement (if initial investment decision was predicated on this)
- (Re)alignment due to technological advances

Basis of FDA Drug Approvals

85 indications for 59 cancer drugs 2006-18,

- 32 (38%) regular approval,
- 53 (62%) accelerated approval.

29 (55%) accelerated approvals were later converted to regular approval. Of these,

- 6 (21%) showed overall survival benefit,
- 16 (55%) later established progression-free survival benefit,
- 7 (24%) continued to use RR but gained regular approval.

Chen EY et al. JAMA doi:10.1001/jamainternmed2019.0583

Risk-sharing and Pricing

- Both flexible regulatory pathways and early access programs change the relationship between the sponsoring company, the regulator, and the payer
- The payer in effect shares a greater proportion of the risks (and possibly benefits) of the uncertainty with the sponsor.
- Governments as payers will expect that the budget consequences of that shared risk is recognised and compensated.
- Entry pricing expectations will be a rate limiting step in uptake of early access programs.

New Challenges in Reimbursing Cancer Treatments

- Combination on-patent medicines
  - Cost-effectiveness
  - Sharing the risk with more than 1 company
- CAR-T (and descendants)
  - Durability of response – when is cure cure?
  - Care costs
  - Upfront cost
- Pan tumour marker therapy
  - Basket trials,
- Precision oncology
  - Assessing the value of individualized therapies

Issues of Biomarker Testing Relevant to Cost-Effectiveness and Costs

- What is the evidence that the biomarker identifies patients who are more likely to respond to a specific therapy rather then tumours that have a better outcome?
- Is the response demonstrated to be limited to tumours expressing the biomarker or is it only quantitatively different?
- What is the prevalence of the biomarker in different tumour types?
- Are there more than one test for the biomarker and if so, what is their concordance?
- What are costs and consequences of tumour biomarker testing (for example the implications of testing for germline mutations for other family members)?
- Is the tumour biomarker stable across disease progression ie can the tumour marker appear denovo or through clonal selection following treatment?

Cost-Effectiveness and Targeting

Ramsay SD et al. JCO
Doi:110.150.005.080

TABLE 1. Clinical and Economic Outcomes in Practice Settings for a Test With 99% Sensitivity and 95% Specificity for a Tumor Mutation at Varying Levels of Mutation Prevalence Across Tumor Types

Clinical and Economic End Points	Cancer Type		
	Non–Small-Cell Lung Cancer	Prostate Cancer	Thyroid Cancer
Clinical end points			
Prevalence of mutation, %	1	10	20
Population, No.	1,000	1,000	1,000
Mutation, No.	10	100	200
No mutation, No.	990	900	800
TP, No.	10	99	198
FP, No.	50	45	40
TP plus FP, No.	60	144	238
F1 score	0.29	0.81	0.90
PPV, %	17	69	83
Economic end points*			
Total cost, targeted therapy strategy, $	26,660,000	32,384,000	28,768,000
Total cost, standard therapy strategy, $	24,000,000	24,000,000	24,000,000
Survival with targeted therapy strategy, life-years gained	1,005	1,094.5	1,194
Survival with standard therapy strategy, life-years gained	1,000	1,000	1,000
Incremental cost effectiveness (cost per life-year gained), $	532,000	88,720	76,124

Abbreviations: FP, false positive; PPV, positive predictive value; TP, true positive.

*Model assumptions: targeted therapy screening test cost, $500; drug cost, targeted, $15,000/month, standard, $4,000/month; treatment duration, responders (targeted and standard), 6 months; treatment duration, nonresponders, 2 months; survival, targeted treatment, 2 years, standard treatment, 1 year; survival decrement, false-positive targeted test, 0.1 years. No difference in lifetime costs of care beyond drug costs.

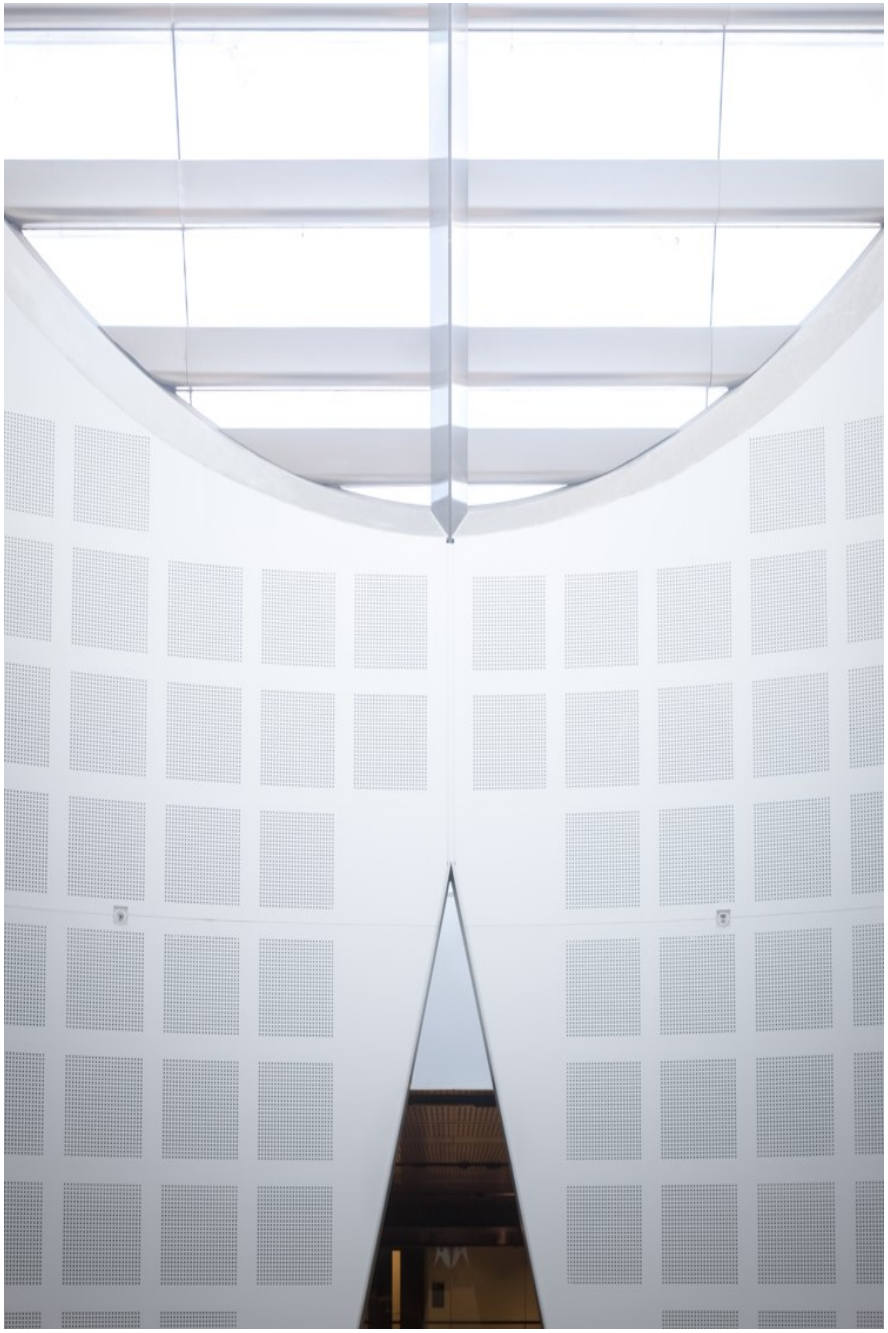
Convincing Data

- Well design trials that address the way a drug is likely to be used in practice.
- Outcome measures that reflect patient-important factors.
- Benefit effects that are clinically meaningful.
- Appropriate consideration of adverse effects.
- Benefits that are measured not claimed.
- Modelled benefits that are realistic given the known history of the disease and patient characteristics.

In Conclusion

- There is increasing pressure to provide access to novel medicines faster.
- Not always clear what Novel means from the perspective of added therapeutic value.
- Novel medicines usually come with greater uncertainty in the evidence of benefit and harm.
- The total cost consequences are becoming greater.
- Future funding for novel therapies is not and will not be limited to the PBS.
- New post PBAC pathways to facilitate assessment of novel medicines with high therapeutic value

Thank-you
Questions?



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