MEDINFO23

8 – 12 JULY 2023 | SYDNEY, AUSTRALIA

@fpylin

Precision oncology: AI-enabled decision support for genomic treatment recommendations by the molecular tumour board

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Disclosures

- None
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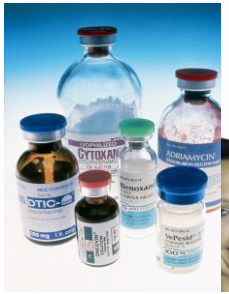
Garvan Institute of Medical Research | Omico. | NHMRC Clinical Trials Centre | The University of Sydney | UNSW Sydney

Evolution of Cancer Therapy

Traditional cytotoxic chemotherapy



Biology-centric & biomarker-linked therapies have replaced traditional drug development

48 newly approved therapies in 2022-2023

38 Approvals in solid cancers

21 (55%) Biomarker-linked therapies

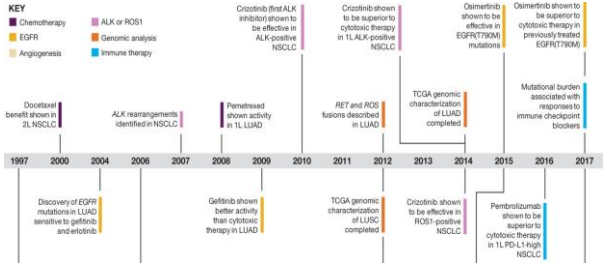
16 (42%) linked to genomic biomarkers

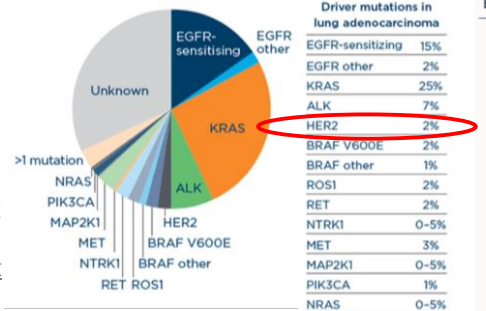
Adapted from *J Clin Invest*. 2022;132(8):e154943; The United States Food and Drug Administration; Wikimedia Commons

NHMRC Clinical Trials Centre Since 1988

Garvan Institute of Medical Research

Genomics has redefined the therapeutic landscape in oncology



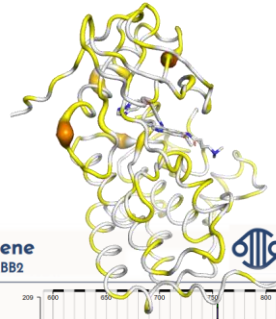


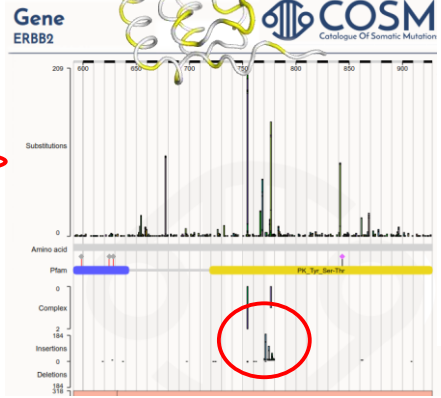
Driver mutations in lung adenocarcinoma

EGFR-sensitizing	15%
EGFR other	2%
KRAS	25%
ALK	7%
HER2	2%
BRAF V600E	2%
BRAF other	1%
ROS1	2%
RET	2%
NTRK1	0–5%
MET	3%
MAP2K1	0–5%
PIK3CA	1%
NRAS	0–5%
>1 mutation	3%
Unknown	31%

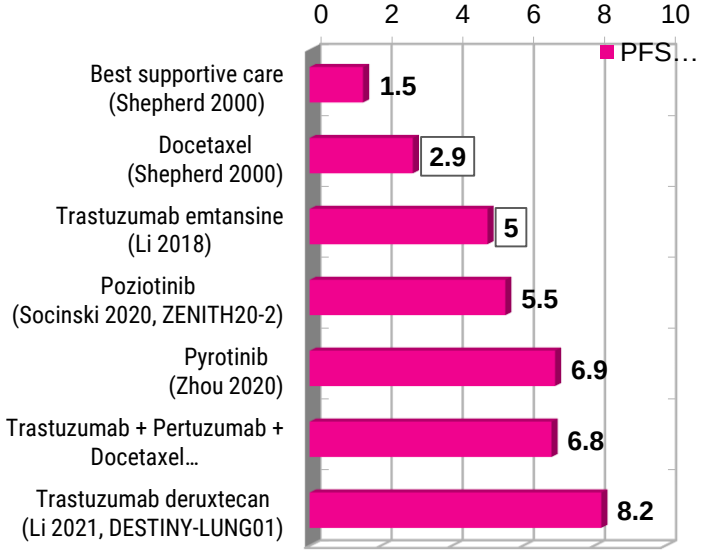
Adapted from Herbst *et al. Nature* 2018; Robichaux, et al. Nat Med 2018; COSMIC

HER2-mutant Non-Small Cell Lung Cancer (NSCLC)

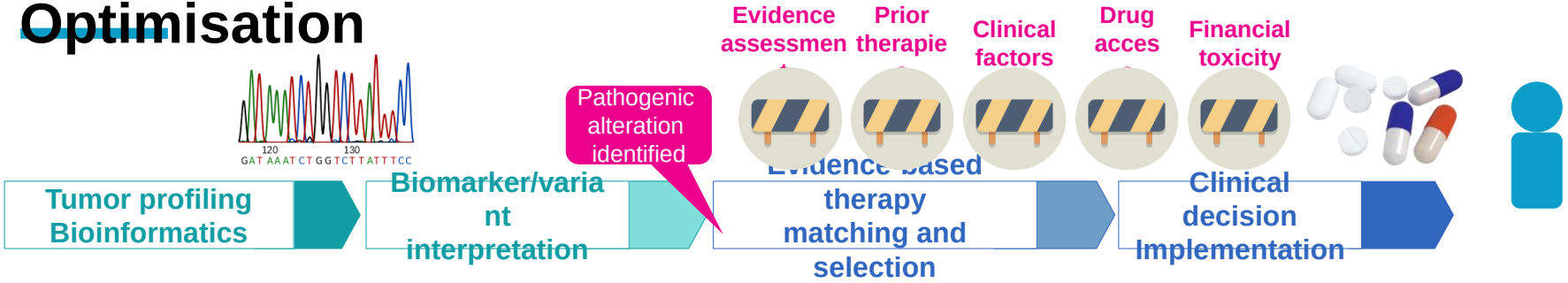




Advances in therapies (Progression-free survival)



Precision Medicine: Information-directed Decision Optimisation



- Genomics - ↑ drug targets for patients with advanced malignancies.
- However, in the case of treatment-refractory cancers, there exists an **information challenge** involving drug selection and finding clinical trials, calling for multidisciplinary input due to the clinical complexity.

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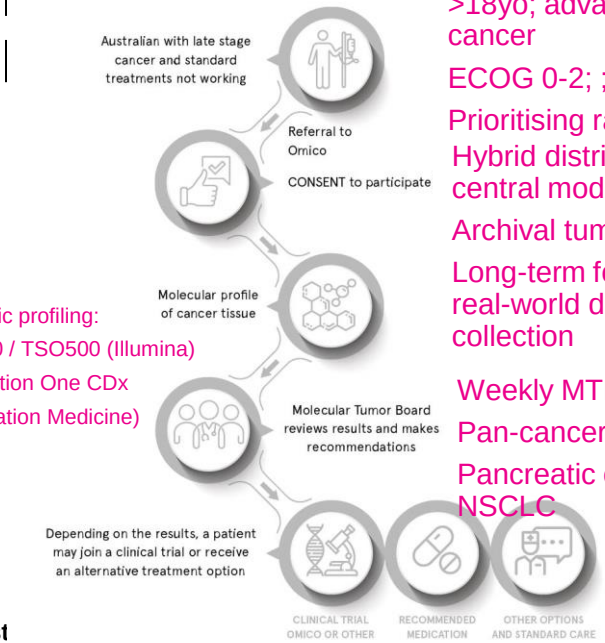
Molecular Screening and Therapeutics (MoST) - National Precision Oncology Research

Prof. David Thomas



Genomic profiling:
TST170 / TSO500 (Illumina)
Foundation One CDx
(Foundation Medicine)

>18yo; advanced and/or poor prognosis cancer

ECOG 0-2; ; suitable for active treatment

Prioritising rare cancers

Hybrid distribute / central model of consent

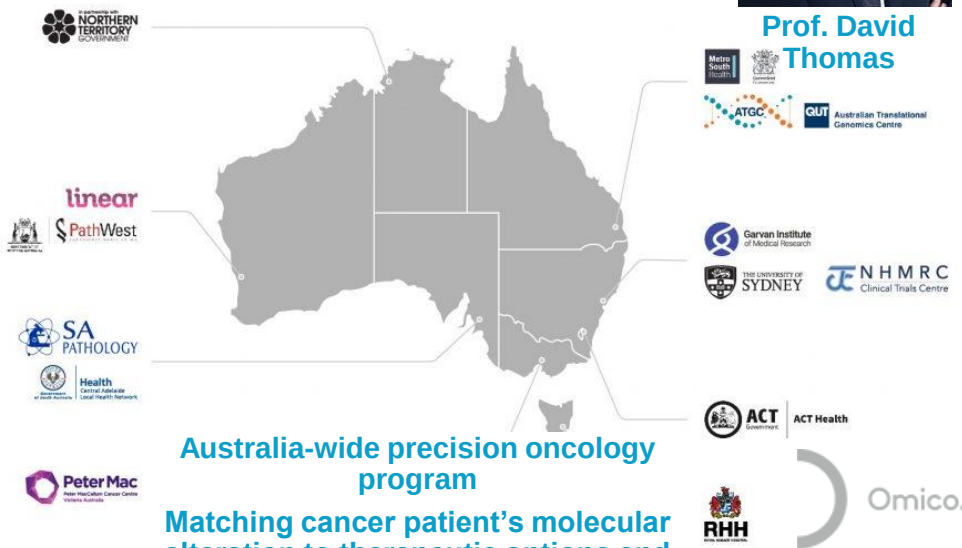
Archival tumour tissue

Long-term follow-up real-world data collection

Weekly MTB, 40-50 cases;

Pan-cancer; Haematology;

Pancreatic cancer; NSCLC



Australia-wide precision oncology program

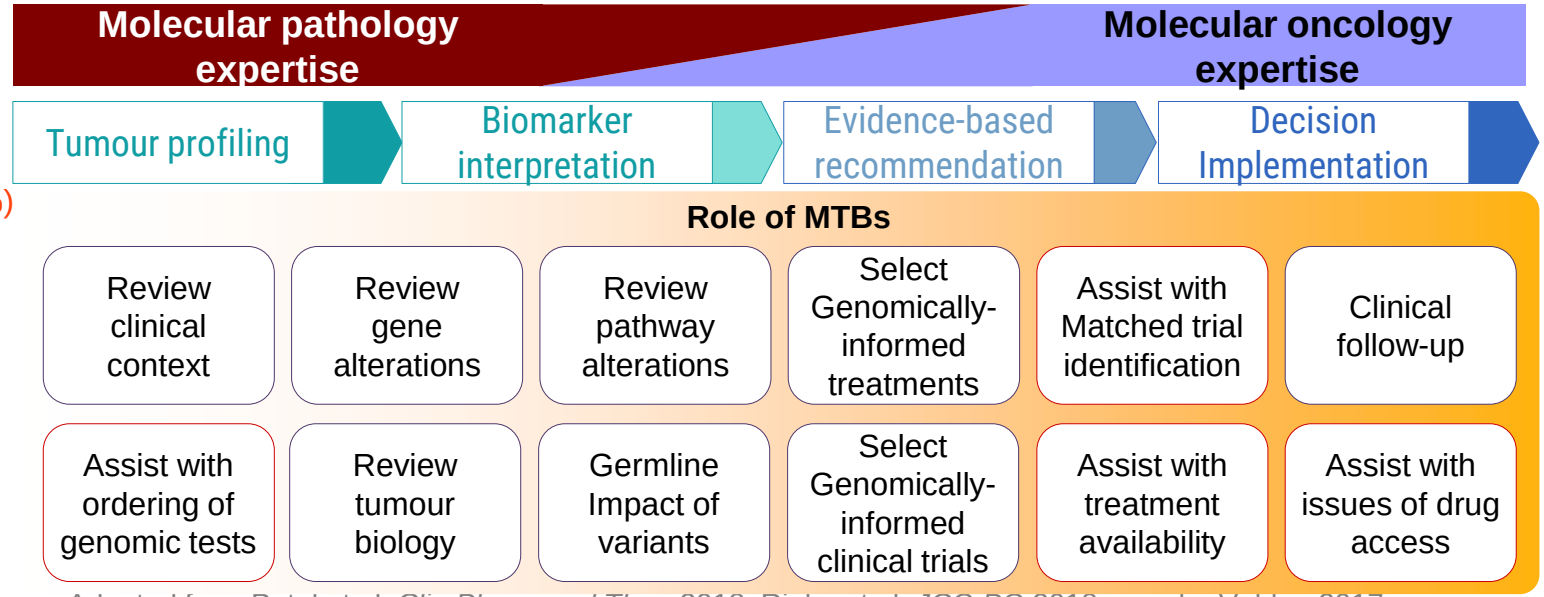
Matching cancer patient's molecular alteration to therapeutic options and

@TheInst

Institutional Molecular Tumour Boards (MTB)

MTB membership:

Oncologist (100%)
Pathologist (91%)
Geneticist (89%)
Bioinformatician (38%)
Mol.biologist (25%)
Pharmacist
Radiologist
Surgeon
Radiation oncologist
Mol. Scientist
Engineer
Nurse coordinator
Patient advocates



Adapted from Patel et al. *Clin Pharmacol Ther*. 2018; Rieke et al, *JCO PO* 2018; van der Velden 2017; 3070
Zeng et al, *JCO Clin Cancer Inform* 2019; Pishvaian et al. *JAMIA Open* 2019.

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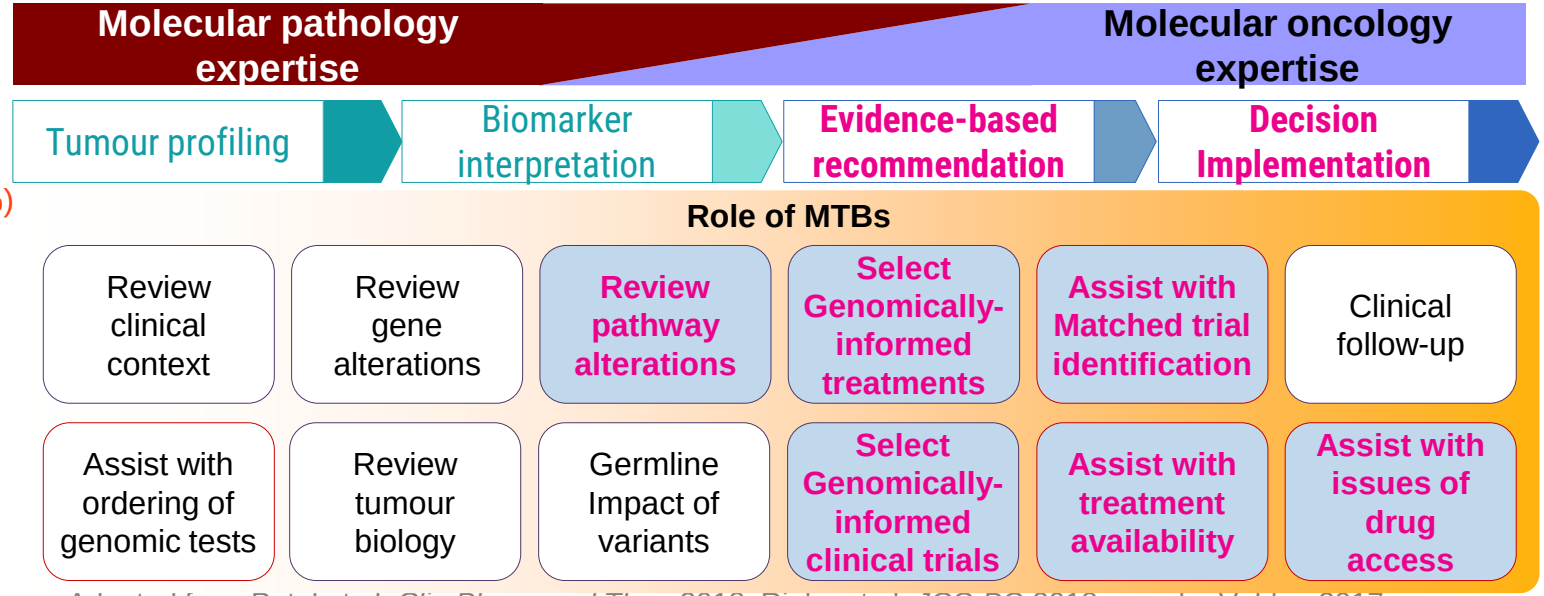

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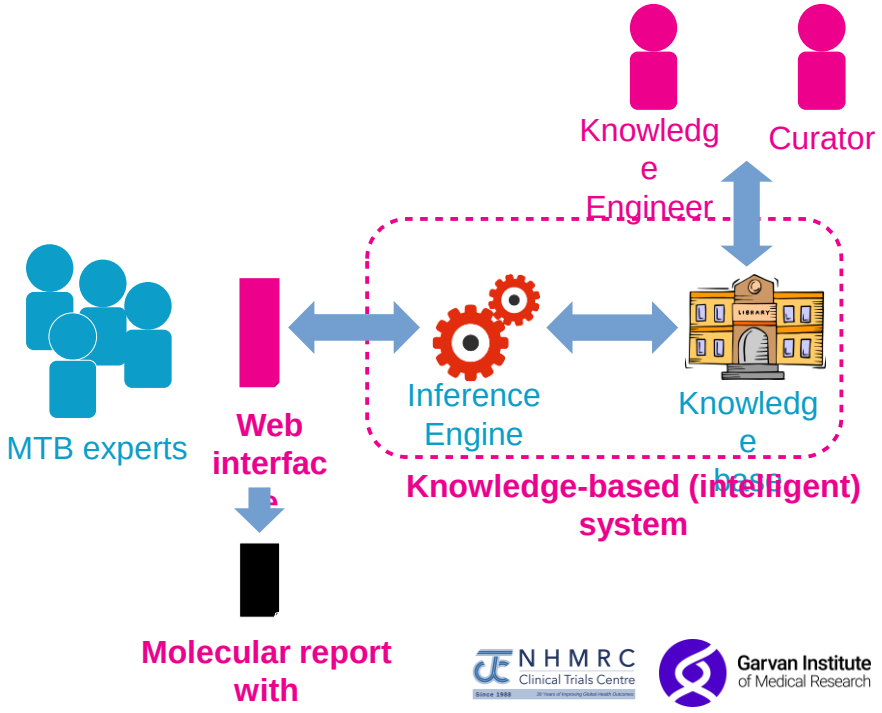
Zeng et al, *JCO Clin Cancer Inform* 2019; Pishvaian et al. *JAMIA Open* 2019.

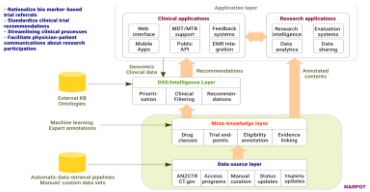
Addressing the Info Need by the MTB: an AI-DSS

Decision support (DSS) design:

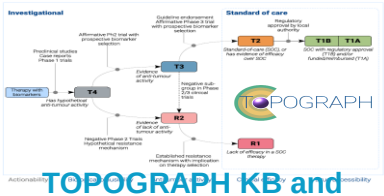
- **Information synthesis** after **variant interpretation**
- **Linking knowledge to action:** Structuring the complex, up-to-date knowledge by linking with an therapy database and annotated trials registry.
- **Interaction with multidiscplinary experts:** A platform for streamlining the **reporting of recommendations, translating** clinicogenomic data onto therapies and trials



AI-DSS: Architecture of MTB support system for MoST



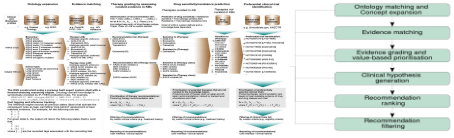
Australian precision oncology trials registry with annotated metadata



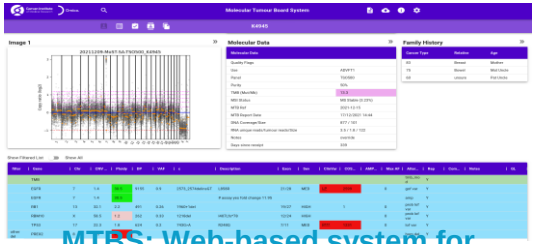
TOPOGRAPH KB and prioritisation strategies for evidence integration

Clinical and somatic genomic profiling data

"Gentian" - the variant interpretation pipeline



Precision oncology treatment and trials recommender - **Symbolic AI engine** for integration of clinicogenomic data



MTBS: Web-based system for virtual multidisciplinary discussion, trial filtering with integrative information display & decision-support interfaces

Precision Oncology Clinical Reporting with Recommendations

AI-DSS (1) : Evidence-based therapy KB

TOPOGRAPH

https://topograph.info/

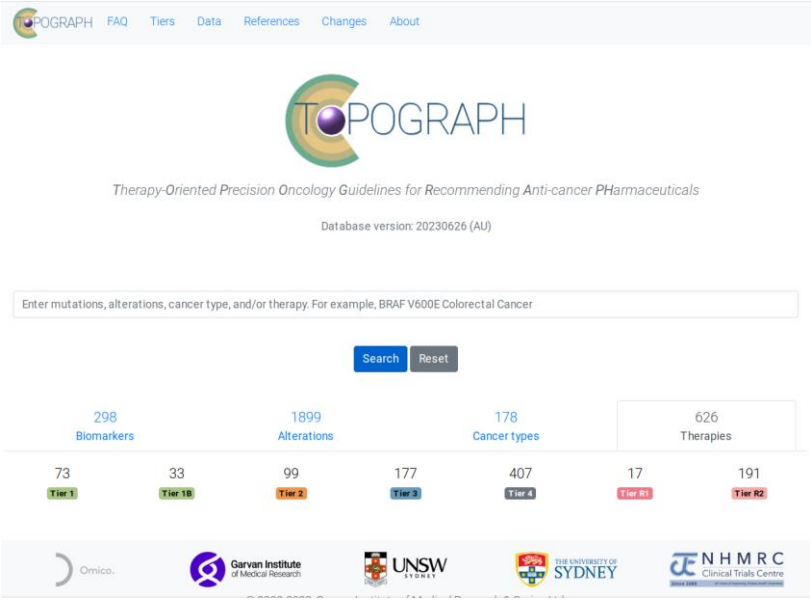
Therapy-focused knowledgebase for precision oncology

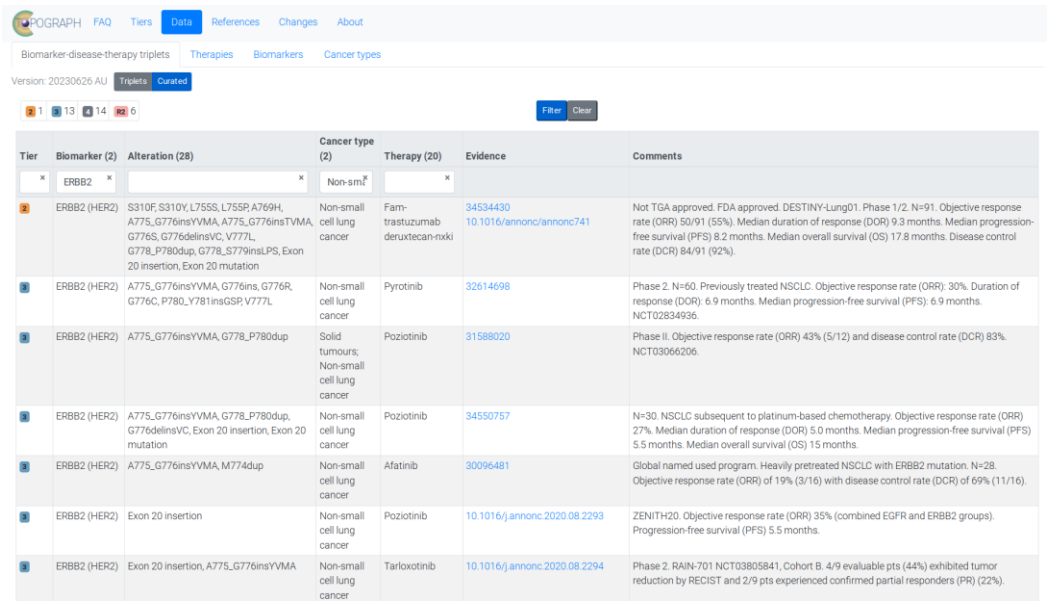
A curated knowledgebase of biomarker-driven therapies for advanced or metastastic cancers in solid tumours

To address the following questions in clinic:
- **Does a therapy work when a biomarker is present/absent?**
- **Are there new therapies?**
- **How does resistance mutation influence drug activity?**
- **How should treatments be prioritised?**

Tumor profiling Bioinformatic analysis → Biomarker/variant interpretation → Evidence-based therapy recommendation → Clinical decision Implementation

AI-DSS (1) : Evidence-based therapy KB

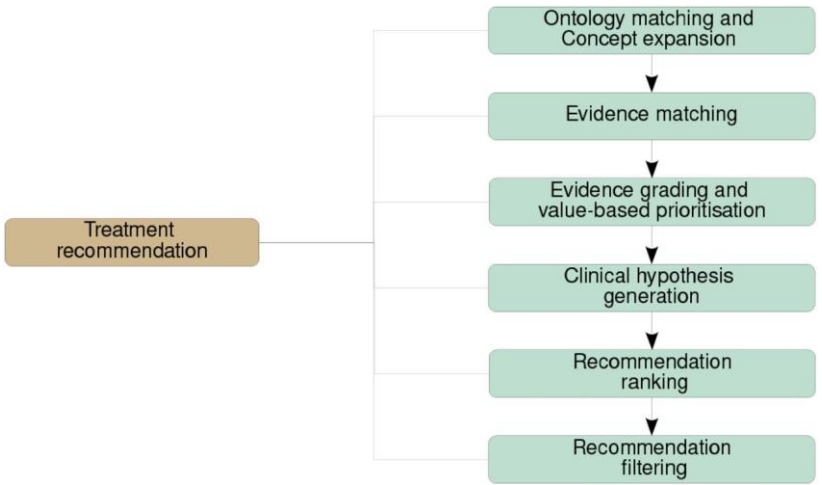




https://topograph.info/; Lin et al. *npj Precis Oncol* 2021; 5: 58

AI-DSS (2): Symbolic AI engine

- Using **hierarchical decision analysis** to model of oncologist's decision-making steps
- Precision Oncology Treatment and Trials Recommender (POTTR)
  - Novel symbolic expert system (ES) as intelligent agent, integrating 10+ databases and ontologies.
  - "White box" system to allow full audit and explicit fine-tuning of recommendations



Lin. *BioXriv* 2020; 10.1101/2020.11.15.383448v1

AI-DSS (2): Symbolic AI engine

Rule-based system
Forward chaining

```
ERBB2:Y772_A775dup => ERBB2:A775_G776insYVMA

catype:NSCLC => catype:DOID:3908

ERBB2:A775_G776insYVMA; catype:DOID:3908 =>
                ERBB2:treatment:Trastuzumab Deruxtecan (TOPOGRAPH LOE: 2)
                                [CERTAIN:treatment; evidence:34534430, 10.1016/annonc/annonc741]

ERBB2:treatment:Trastuzumab Deruxtecan (TOPOGRAPH LOE: 2)
                => recommendation_tier:Trastuzumab Deruxtecan:2

recommendation_tier:Trastuzumab Deruxtecan:2
                => sensitive_to:Trastuzumab Deruxtecan

sensitive_to_drug_class:anti-ERBB2_antibody-drug_conjugate; NOT therapy_sens_predicted:Trastuzumab Deruxtecan; NOT
resistant_to_drug_class:anti-ERBB2_antibody-drug_conjugate; NOT resistant_to:Trastuzumab Deruxtecan; sensitive_to:Trastuzumab Deruxtecan =>
therapy_sens_predicted:Trastuzumab Deruxtecan; sensitive_to:Trastuzumab Deruxtecan

sensitive_to:Trastuzumab Deruxtecan
                =>              therapy_recommendation:Trastuzumab Deruxtecan:2

sensitive_to_drug_class:anti-ERBB2_antibody-drug_conjugate; catype:DOID:3908; ERBB2:oncogenic_mutation; NOT EGFR:oncogenic_mutation; NOT
BRAF:oncogenic_mutation; NOT ALK:fusion; NOT ROS1:fusion; *NOT prior_therapy:ALK_inhibitor; *NOT prior_therapy:BRAF_inhibitor; *NOT
prior_therapy:platinum-based_antineoplastic_agent
                => preferential_trial_id:NCT04644237
```

Variant normalisation

Ontology mapping / expansion

Evidence matching

60,000+ production rules
10+ Ontologies

Recommendation tiering/ LOE assignment against TOPOGRAPH

Drug sensitivity prediction (direct)

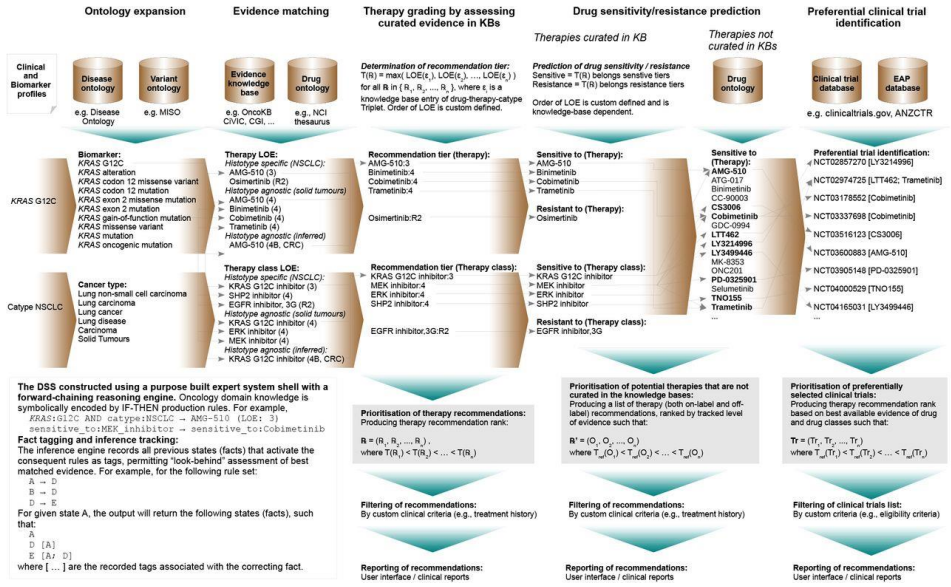
Drug sensitivity prediction (indirect)

Therapy recommendation

Preferential trial identification and prioritisation

AI-DSS (2): Symbolic AI engine

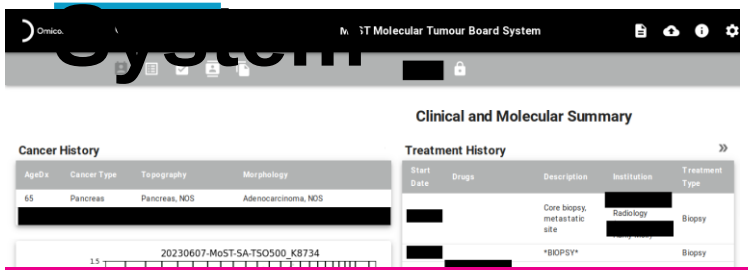
Value-based prioritisation



- Variant-variant interaction
- Variant-clinical variable interaction
- Boolean logic inference
- Treatment options prioritized by evidence-based strength of recommendation algorithm
- Entire hypothesis state-space is evaluated
- Inference tracking allows rational prioritisation and explanability
- Identification of evidence gap through contingency reasoning

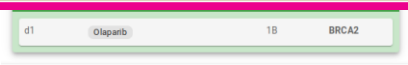
Lin. *BioXriv* 2020; 10.1101/2020.11.15.383448v1

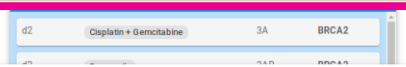
AI-DSS (3): Virtual MTB and Reporting



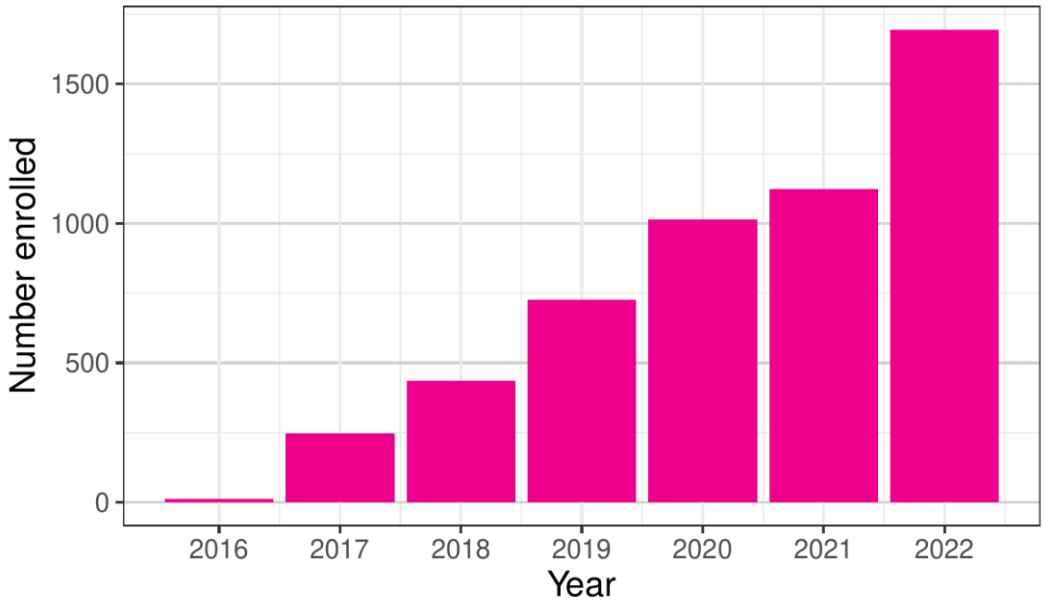
gene	chr	cnv_size	copy_no	dp	vaf	c	description	exon	sev	clinvar	cosmic	alterati…
BRCA2	13	21.12	1.8	1052	0.53	4284dup	Q1429Sfs*9	11/27	HIGH	P***		lof var
CDKN2A	9	38.61	0.8	254	0.21	247C>T	H83Y	2/3	MED	U*	139	lof var
KRAS	12	18.58	0.9	802	0.17	34G>C	G12R	2/5	MED	P*	1603	gof var
RNF43	17	23.07	1.0	1071	0.14	450+1G>A			HIGH			prob lo…
SMAD4	18	57.21	1.9	966	0.27	1082G>A	R361H	9/12	MED	P**	183	lof var
TP53	17	22.26	1.3	1025	0.14	724T>C	C242R	7/11	MED	CP*	16	prob lo…

Prior to DSS implementation	After DSS implementation (New clinical report)
Drug class recommendations	**Specific drug and class recommendations**
No clinical trial recommendations	**Specific trial recommendations with evidence-based prioritisation**
Tiering through MTB consensus	**Tiering through evidence-based knowledge base (KB) and symbolic AI**





Results – Impact on Scalability of Research and Services

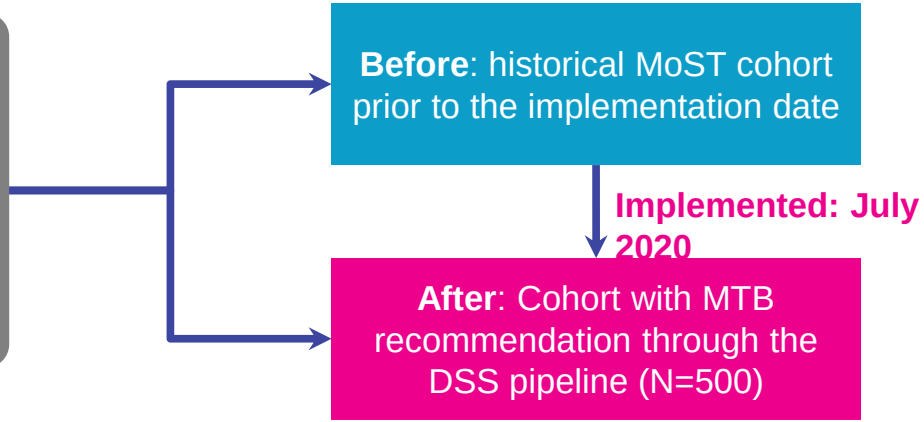


- Ensuring accurate and contemporaneous recommendations based on clinicogenomic profile
- Successful implementation at a national level, now enrolled over 7,000 Australian patients with refractory advanced cancer
- Increased weekly case numbers reviewed by the board ten-fold over 6 years

Results – Schema of Before-After Implementation Study

Inclusion criteria:

- Adult patients (age ≥ 18 years) with treatment refractory solid tumours.
- Referred to MoST for molecular screening and received a report.
- Patients <u>without</u> a matched or ineligible to participate in a MoST molecular matched substudy.



Objective:
- To examine the utility and impact of systematic treatment and trial recommendation system by a MTB in patients with treatment-refractory cancers.

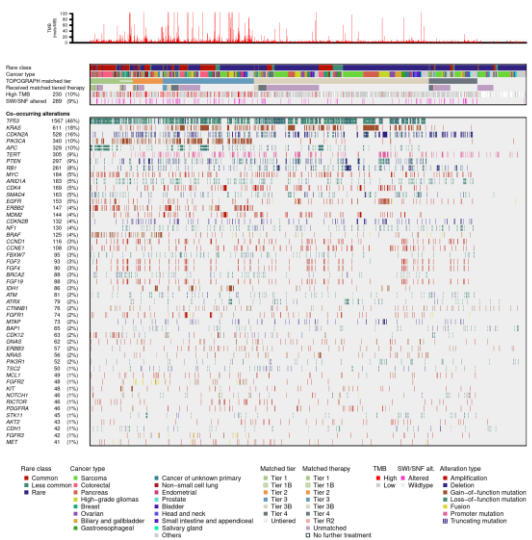
Study design:
- Retrospective Cohort Study in the MoST program populations

Primary endpoint:
- Rate of patients participated in biomarker-linked clinical trials after genomic profiling

Secondary endpoints:
- Rate of patients participated in any clinical trials after profiling
- Overall survival (OS) from the first subsequent therapy following sequencing

Preliminary and unpublished results. Please do not

Preliminary Results: Study Cohort



4,173 patients with rare and refractory solid tumours enrolled through MoST program (2016-2021)

3,383 were alive and had valid genomic sequencing results

1,318 received >=1 line of systemic therapy after molecular profiling

171 received MTB recommend-ations and participated in research program-specific trials

1,147 received therapy where recommendation was not specific to a research program

Preliminary and unpublished results. Please do not

Preliminary Results: Impact on Trial Participation

Biomarker-matched clinical trials:

Cohort	Total	Received
Before DSS implementation	843	43 (5.1%)
After DSS implementation	298	24 (8.1%)

Chi-square test, df=1, p=0.085

Any clinical trials:

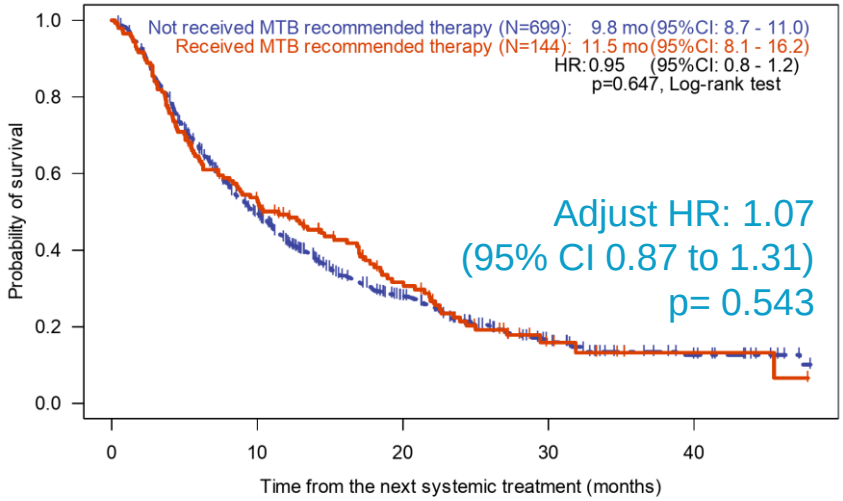
Cohort	Total	Received
Before DSS implementation	843	126 (14.9%)
After DSS implementation	298	61 (20.5%)

Chi-square test, df=1, p=0.034

Preliminary and unpublished results. Please do not share

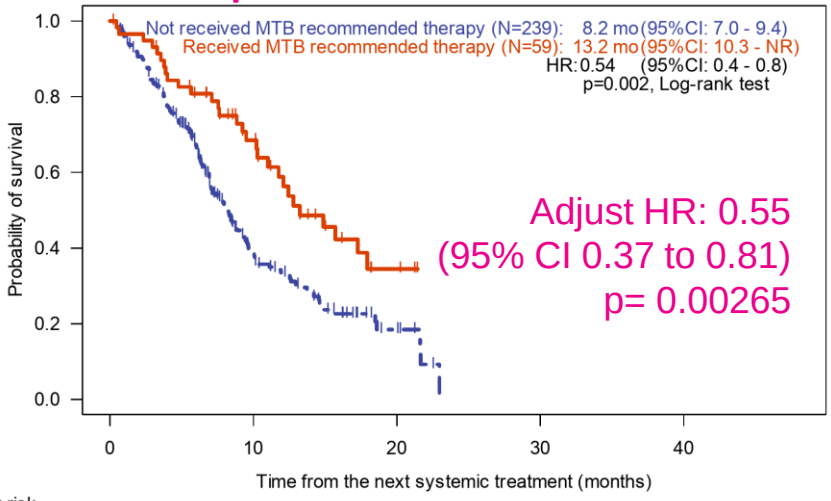
Preliminary Results: Survival Outcomes

Prior to DSS implementation



No. at risk					
Not recv'd rec'd	699	319	132	45	18
Recv'd rec'd	144	74	34	9	6

After DSS implementation



No. at risk					
Not recv'd rec'd	239	57	10	1	1
Recv'd rec'd	59	32	9	9	9

Preliminary and unpublished results. Please do not share

Summary

- AI-enhanced DSS plays a crucial role by facilitating multidisciplinary decision-making through structured treatment and trial recommendations.
  - Provides timely recommendations to referring oncologists, potentially improving trial participation and survival outcomes in patients with refractory cancer.
- Through enhanced recommendation accuracy and efficiency, AI-DSS utilisation has facilitated the expansion of research programs to a national scale, enabling seamless handling of substantial volumes.
- The benefits of integrating DSS into precision cancer medicine will be determined through further analysis and prospective studies.

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Jayesh Desai
Stephen Fox
Stephen Luen
Andrew Fellowes
Huiling Xu
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Hamish Scott
Princess Alexandra Hospital, QLD
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Michail Charakidis

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Michelle Wilson

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Damien Kee
Maureen Turner
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Astra-Zeneca, Bayer, Eisai, Pfizer, Roche
MoST patients/participants
Referring Clinicians
Co-investigators

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Consumer Groups
Rare Cancers Australia
CanTeen, CanToo
Cancer Voices
Brain Tumour Alliance Australia
Pancare Foundation

Email: f.lin@garvan.org.au @fpylin

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