

Drug Repurposing



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Drug repurposing – definition

-  <https://remedi4all.org/>

- **Drug repurposing – approved product**

Finding a new use/indication for an existing/licensed medicinal drug product (applying approved dosage forms/strengths).

- **Drug repositioning/rescue – known safe substance**

Finding a new use/indication for a (de-risked) drug molecule (i.e., drug substance for which human safety data are available).




Anticancer Fund

Using what we have, to treat who needs it

- Old
- Universal
- Drug repositioning (Ashburn 2004) followed by drug repurposing (Carley 2005)
- Successful examples before it was officially born
 - Aspirin, lidocaine, propranolol ... in 2nd half of 20th century
 - Thalidomide & Viagra in the 1990s → viable commercial model

Clinical data as main driver

- Initial signal is clinical for 57% of new uses (DeMonaco 2006)
- From clinicians & patients
 - “Desperate” attempts: leprosy symptoms relieved by thalidomide (Sheskin 1965)
 - Astute observations: infantile haemangioma regression on propranolol (Leauté-Labreze 2008)
 - Patient: migraine relief with propranolol (Rapkin 1966)
 - Secondary analysis of data: aspirin and colorectal cancer incidence (Kune 1988)

Scientific knowledge to inform repurposing

- Turn of the 21st century
- Scientific converging arguments
 - Better knowledge of drugs
 - Better knowledge of diseases
 - Contribution from multiple disciplines
- Examples
 - Imatinib to target c-kit in gastro-intestinal stromal tumours
 - Rituximab to target B-cells in 'auto-immune' diseases

Scale of 'new indications or uses'

FDA 2004 drug cohort

34 products

Excluded (n=6)

3 products use for imaging,
3 fully suspended

28 eligible

		New indication		
		0	≥ 1	
Off-label	0	13	8	21
	≥ 1	3	4	7
		16	12	



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Off-label	0	13	8	21
	≥ 1	3	4	7
		16	12	

12 with ≥ 1 formal new indication

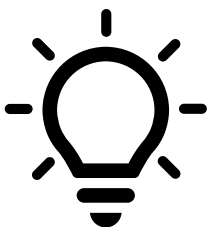
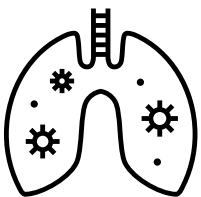
7 with ≥ 1 common off-label indication

15 products ≥ 1 new use

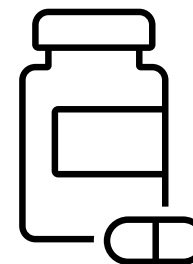
Notable examples: duloxetine, natalizumab, pregabalin, trospium chloride

PRESENT

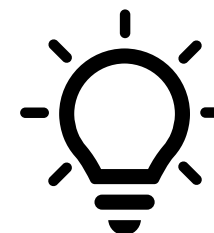
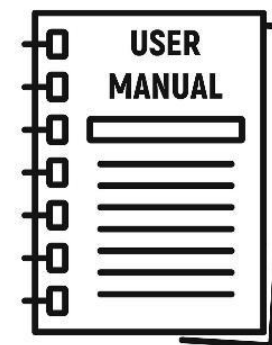
Finding an existing drug to address a biological problem



Finding a disease that a drug could help fixing



approved



Toolbox has the adequate tool

- Alpelisib: breast cancer drug → 1st disease-modifying drug for PIK3CA-related overgrowth syndrome

Day 0



Day +180

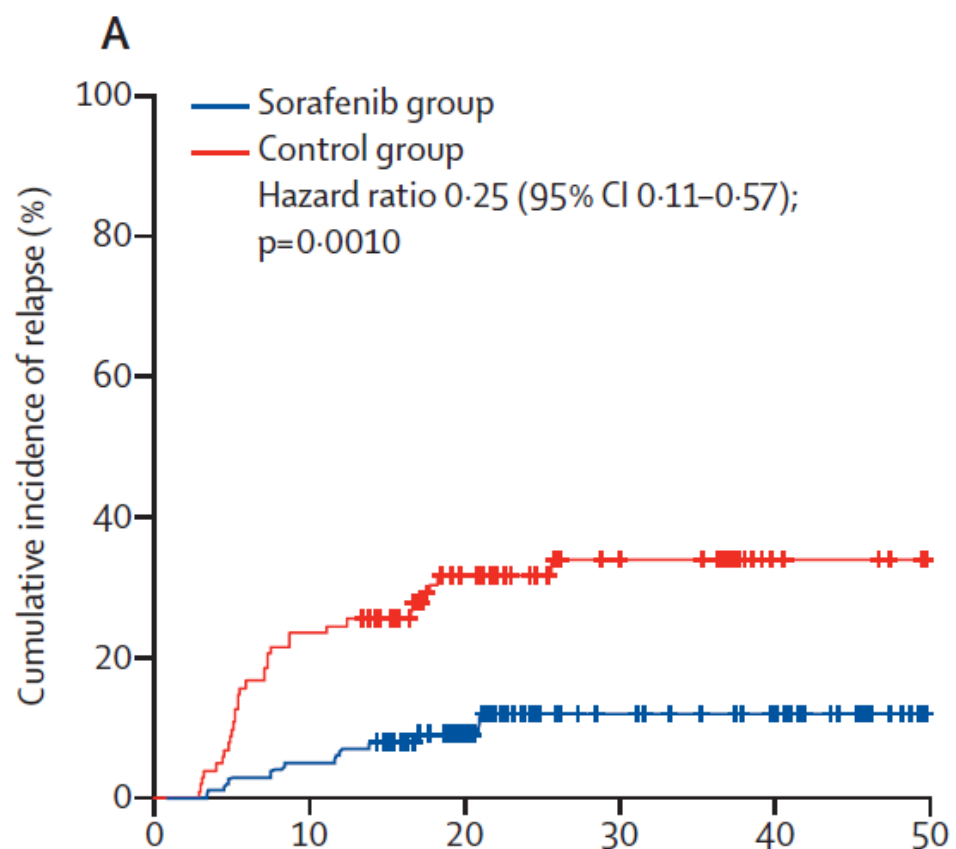


Day +2292

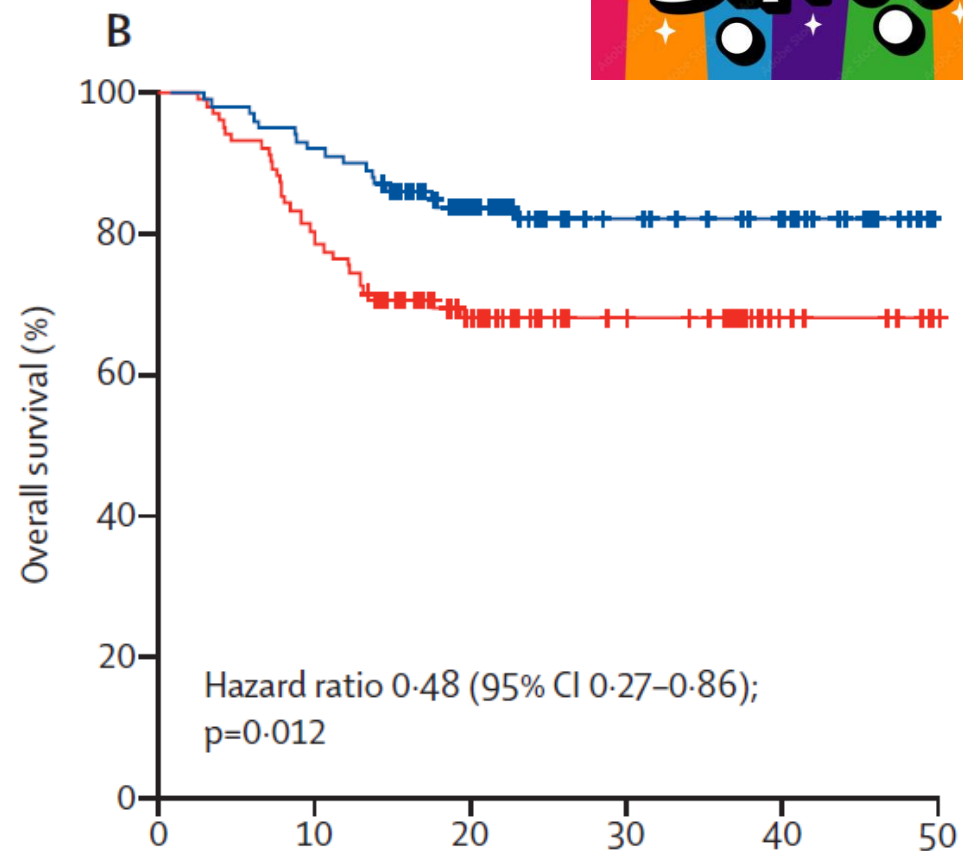


Listen to the drug

- Sorafenib (Nexavar, Bayer), generic products since 2020
 - First approval in 2006 (liver cancer)
 - A multi-kinase inhibitor (BRAF, KIT, FLT3, VEGFR2 & 3, PDGFR- β)
 - Acute myeloid leukaemia (AML) work from 2002 including 2 German randomised trials
- Key findings in AML
 - Good FLT-3 inhibitor
 - Effect post-transplant because it promotes Graft vs Leukaemia effect (Mathew 2018 Nat Med)



Number at risk (number censored)							
Sorafenib group	100 (0)	90 (0)	62 (20)	33 (47)	23 (57)	0 (80)	
Control group	102 (0)	68 (0)	37 (22)	21 (37)	6 (52)	0 (58)	



Number at risk (number censored)							
Sorafenib group	100 (0)	92 (0)	64 (20)	33 (50)	23 (60)	0 (83)	
Control group	102 (0)	81 (0)	48 (22)	30 (40)	10 (60)	1 (69)	

(Too?) many opportunities

- 2,000 approved drugs * 10,000 diseases = 20 million possibilities
- Many valid hypotheses
 - Mechanistic thinking, analogy, AI ...
 - High-throughput screening, phenotypic assays, in vivo models ...
 - Electronic medical records, pharmaco-epidemiology ...
- Eventually wrong in >90% of the time
- We don't have the recipe

Greater & greater interest

- Every drug
 - is hard and costly to develop
 - will reveal features we don't know yet
- Duty = getting the best from existing medications
 - Find the patients they can help
 - Find more about the tricks they hide
- Pandemics, neglected disease: what else?



Challenges (1) – Scientific

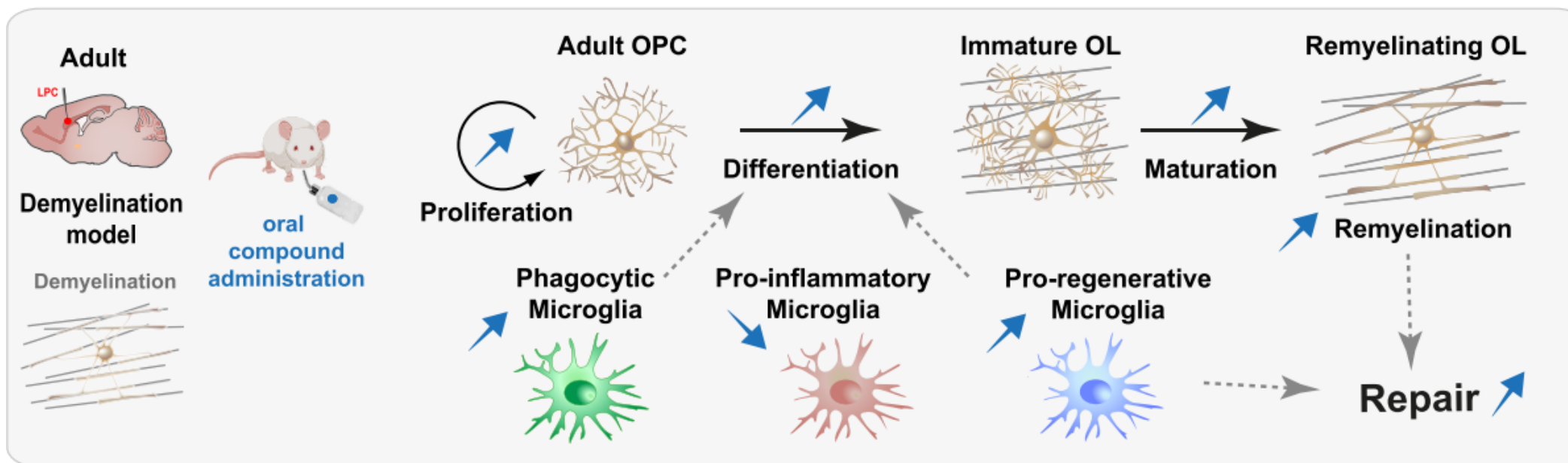
- Limitations of preclinical research and animal models
- Noise vs. signal in published data
- Wrong biological, pharmacological and clinical assumptions
- Choice of candidates
 - >300 active trials with metformin
 - MND-SMART: top 2 candidates memantine and trazodone failed (Wong 2023 BMJ Open, Pal 2024 Lancet Neurol)

Challenges (2) – Evidence generation

- Transfer of knowledge to whom might need it
- Trial readiness / reactivity to new knowledge
- Too many trials that say “maybe” (Carlisle 2018 BMJ)
- Funding models inappropriate
 - Rarely commercially viable
 - Grant model is rather slow and inefficient

Challenges (2) – Evidence generation

Leucovorin in Multiple Sclerosis (Huré 2024 Nat Commun)

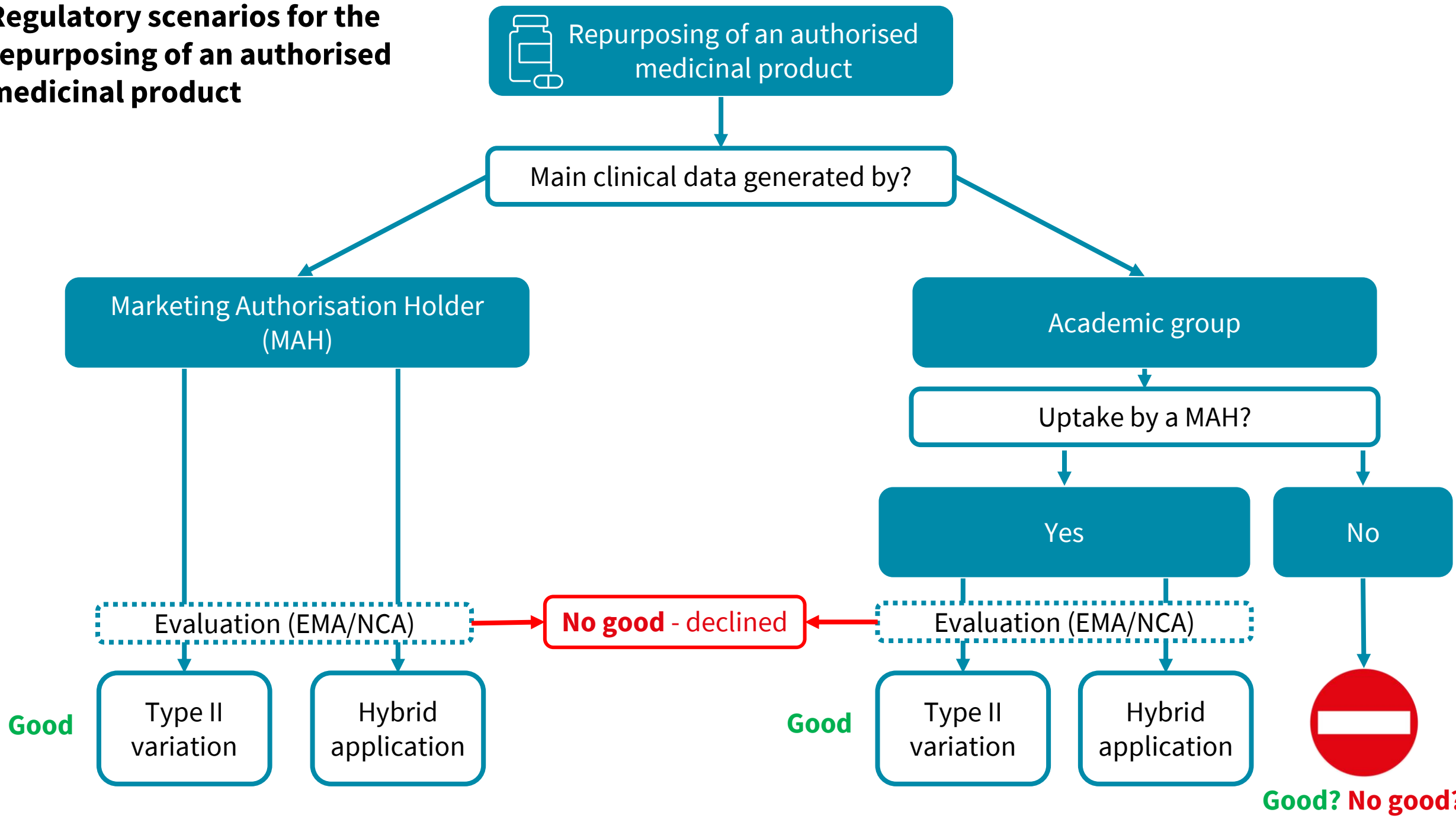


Article submitted 3 May 2023, published on 13 Nov 2024

Challenges (3) – Regulatory

- Regulatory pathways
- Collaboration between marketing authorisation holder and academia
- Liability

Regulatory scenarios for the repurposing of an authorised medicinal product



Sorafenib in FLT3-*ITD* AML – Off-label



- Covered by insurance since 2022. BfArM endorsement of off-label use in July 2024.



- Positive NHS commissioning in Nov 2023



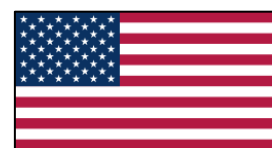
- Prescription at the full expense of the National Health Service in 2024



- “We prescribe it, and patients get it” since 2022



- Not evaluated. A chapter IV drug. Individual justification needed.



- Covered since in NCCN guidelines (Bouche 2021 Nat Rev Clin Oncol)

Major initiatives around repurposing

Name	Country	Discovery	Clinical dev.	Implementation
New Therapeutic Use (NCATS/NIH)	US	✓	✓	
MRC-AZ collaboration	UK	✓		
REPO4EU	EU	✓		
REMEDI4ALL	EU	✓	✓	✓
CURE Drug Repurposing Collaboratory (FDA)	US		✓	
NHS England medicines repurposing programme	UK			✓
EMA-HMA repurposing pilot project	EU			✓

NHS medicines repurposing programme

- Triggered by Association of Medical Research Charities [report](#)
- Led by the **NHS** and supported by the DHSC, **MHRA**, **NICE**, and **NIHR**
- Candidates selected through open submission or internally
- 1 official licensing – anastrozole to prevent BC in high-risk patients
 - Open tender → Accord was selected, and cost was covered by NHS
 - Other MAHs invited to update products with access given to dossier
- Pipeline of candidates ([link](#))

REMEDi4ALL PARTNERS & ASSOCIATED PARTNERS



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European infrastructure
for translational medicine

teamit
RESEARCH



This project has received funding from the European Union's Horizon Europe research and innovation programme under grant agreement No 101057442.

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PAST

PRESENT

FUTURE



PROGRESS





Future looks bright – Science

- More scientifically sound repurposing than ever
- Scientific knowledge and tools improving
 - *good* AI: TxGNN (Huang 2024 Nat Med), Kantify (ESMO Sarcoma 2024)
 - ‘Precision’ repurposing (Saez-Atiensar 2024 Cell Genomics)

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TxGNN, what drug can be potentially repurposed for Ehlers–Danlos syndrome?



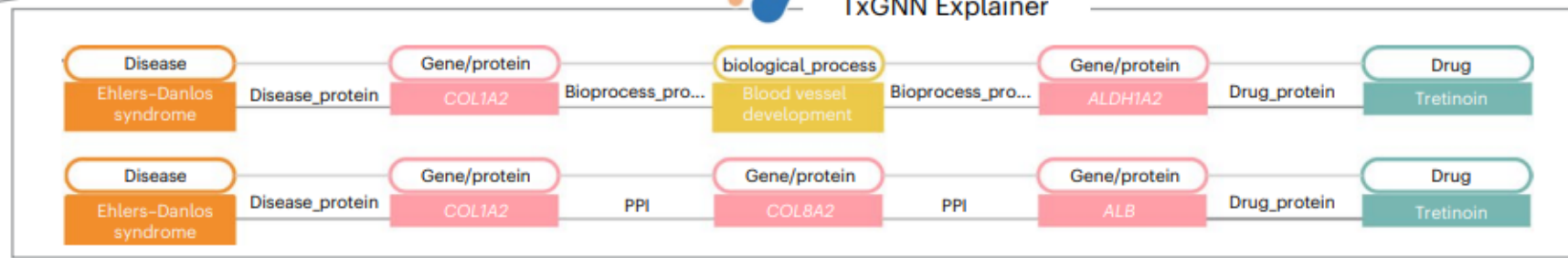
Tretinoin
Score: 0.951
Rank: 1



Why is tretinoin predicted as a repurposing candidate for this syndrome?



TxGNN Explainer

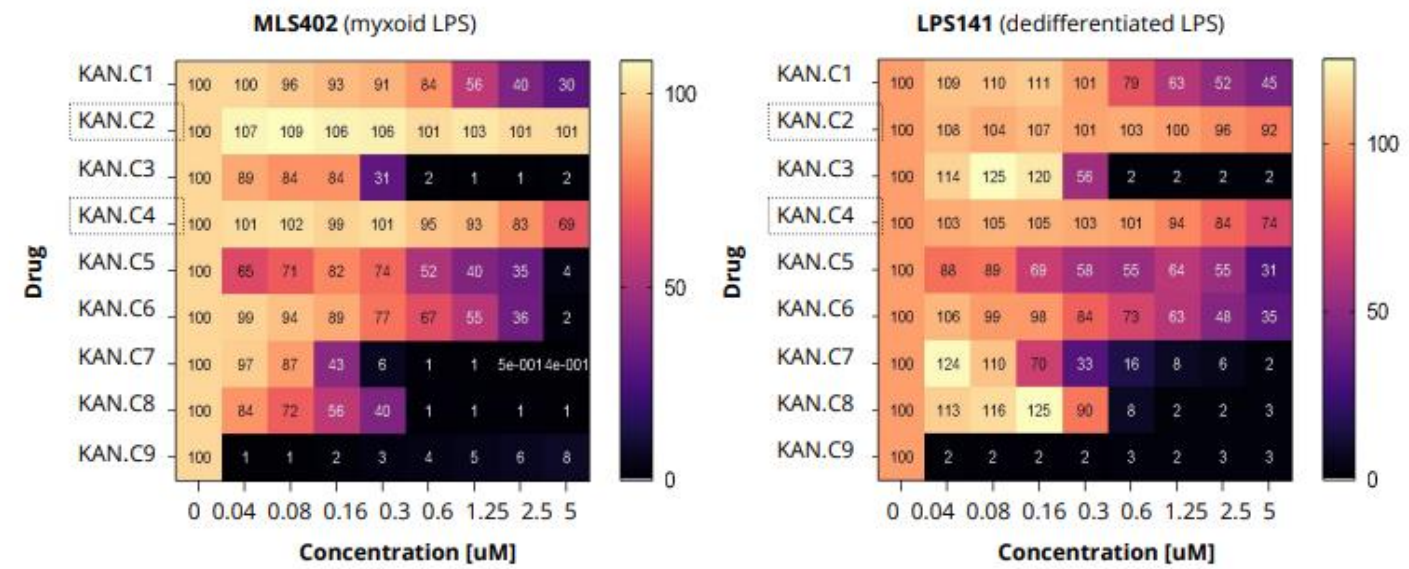


Medical reasoning



Ehlers–Danlos syndrome is a rare connective tissue disorder caused by mutations in collagen-coding genes (*COL1A1*/*COL1A2*) that lead to poor wound healing and abnormal scars. Tretinoin, a Vitamin A derivative, carried by albumin (*ALB*) and acting on *ALDH1A2*, may help improve these symptoms by promoting collagen production in the skin. In ClinVar, Ehlers–Danlos subtypes are linked to *ALB* mutations associated with *ALDH1A1*.

5 7 OUT OF 9 SHORTLISTED DRUGS ARE EFFECTIVE IN REDUCING LPS CELL VIABILITY

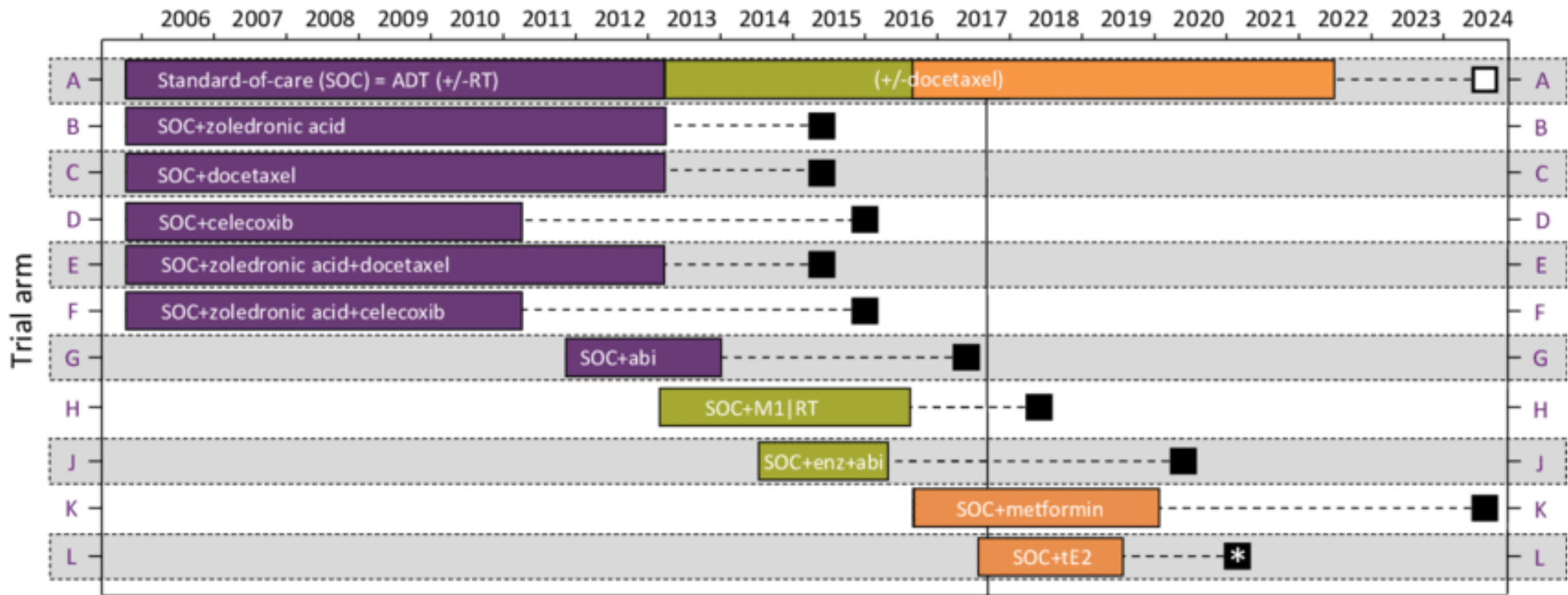




Future looks bright – Evidence

- Growing number of repurposing trials
- Strong interest from funders
 - Public funders: KCE (BE), ZonMW (NL), PHRC (FR), NIHR (UK)
 - Charities
- More efficient trial designs
 - Multi-arm multi-stage trials
 - Basket trials

The STAMPEDE multi-arm multi-stage trial



Abbreviations

Abi = Abiraterone
Enz = Enzalutamide
M1|RT = Prostate RT for M1 prostate cancer
tE2 = Transdermal oestrogens
SOC = Standard-of-care



Smarter Studies
Global Impact
Better Health





Future looks bright – Regulation

- Article 48 of the new EU pharmaceutical regulation
- NHS England repurposing programme (+ Australia)
- Marketing authorisation holders showing more interest
 - Accord in NHS medicines repurposing programme
 - Medicines for Europe work in REMEDi4ALL



Article 48 of the proposed EU regulation

- A 'not-for-profit entity' may submit to the Agency [...] substantive non-clinical or clinical evidence for a new therapeutic indication
- The Agency may, [...] on the basis of all available evidence make a scientific evaluation of the benefit-risk of the use of a medicinal product with a new therapeutic indication
- The opinion of the Agency shall be made publicly available [...]
- In cases where the opinion is favourable, MAH of the medicinal products concerned shall submit a variation to update the product information with the new therapeutic indication.

Key message 1 – Treatment may already lay there

9 weeks of age

On corticosteroids



Léauté-Labrèze 2008 NEJM

6 months of age

On propranolol – Off corticosteroids



Key message 2 – Repurposing is the most efficient strategy



RECOVERY

Randomised Evaluation of COVID-19 Therapy

2 years on





THANK YOU

Questions and comments welcome now
or later at gauthier.bouche@anticancerfund.org



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