Reproducibility in the alignment of the individual human patient and the “precise” animal model
1: the paradox of PM
1) smaller samples
2) edges
Alleles (of unknown significance)
3) algorithms & interpretation
Molecularly targeted therapy based on tumour molecular profiling versus conventional therapy for advanced cancer (SHIVA): a multicentre, open-label, proof-of-concept, randomised, controlled phase 2 trial

Christophe Le Tourneau, Jean-Pierre Delord, Anthony Gonçalves, Céline Gavoille, Coraline Dubot, Nicolas Isambert, Mario Campone, Olivier Trédan, Marie-Ange Massiani, Cécile Mauborgne, Sébastien Armanet, Nicolas Servant, Ivan Bièche, Virginie Bernard, David Gentien, Pascal Jezequel, Valéry Attignon, Sandrine Boyault, Anne Vincent-Salomon, Vincent Servois, Marie-Paule Sablin, Maud Kamal, Xavier Paoletti, for the SHIVA investigators
A classification system for clinical relevance of somatic variants identified in molecular profiling of cancer

Mahadeo A. Sukhai, PhD\textsuperscript{1,4}, Kenneth J. Craddock, MD\textsuperscript{1,4}, Mariam Thomas, PhD\textsuperscript{1,4},
Aaron R. Hansen, MD\textsuperscript{2,4}, Tong Zhang, MD\textsuperscript{1,4}, Lillian Siu, MD\textsuperscript{2,4},
Philippe Bedard, MD\textsuperscript{2,4}, Tracy L. Stockley, PhD, FCCMG\textsuperscript{1,3,4} and
Suzanne Kamel-Reid, PhD, FACMG\textsuperscript{1,3,4}
“We established a minimum level of evidence required to demonstrate clinical actionability… whereby preclinical, biochemical, and in silico data were considered to be insufficient to infer actionability…. There are concerns about … the lack of reproducibility of preclinical experiments.”
Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer

A Joint Consensus Recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists
Tier I: Variants of Strong Clinical Significance

*Therapeutic, prognostic & diagnostic*

- **Level A Evidence**
  - FDA-approved therapy
  - Included in professional guidelines

- **Level B Evidence**
  - Well-powered studies with consensus from experts in the field

Tier II: Variants of Potential Clinical Significance

*Therapeutic, prognostic & diagnostic*

- **Level C Evidence**
  - FDA-approved therapies for different tumor types or investigational therapies
  - Multiple small published studies with some consensus

Tier III: Variants of Unknown Clinical Significance

Not observed at a significant allele frequency in the general or specific subpopulation databases, or pan-cancer or tumor-specific variant databases

- **Level D Evidence**
  - Preclinical trials or a few case reports without consensus
Whole-exome sequencing and clinical interpretation of formalin-fixed, paraffin-embedded tumor samples to guide precision cancer medicine

Eliezer M Van Allen\textsuperscript{1,2,8}, Nikhil Wagle\textsuperscript{1,2,8}, Petar Stojanov\textsuperscript{1,2}, Danielle L Perrin\textsuperscript{2}, Kristian Cibulskis\textsuperscript{2}, Sara Marlow\textsuperscript{1,2}, Judit Jane-Valbuena\textsuperscript{1,2}, Dennis C Friedrich\textsuperscript{2}, Gregory Kryukov\textsuperscript{2}, Scott L Carter\textsuperscript{2},
4) rapid evolution of techniques
Molecularly targeted therapy based on tumour molecular profiling versus conventional therapy for advanced cancer (SHIVA): a multicentre, open-label, proof-of-concept, randomised, controlled phase 2 trial

Christophe Le Tourneau, Jean-Pierre Delord, Anthony Gonçalves, Céline Gavoille, Coraline Dubot, Nicolas Isambert, Mario Campone, Olivier Trédan, Marie-Ange Massiani, Cécile Mauborgne, Sebastien Armanet, Nicolas Servant, Ivan Bièche, Virginie Bernard, David Gentien, Pascal Jezequel, Valéry Attignon, Sandrine Boyault, Anne Vincent-Salomon, Vincent Servois, Marie-Paule Sablin, Maud Kamal, Xavier Paoletti, for the SHIVA investigators
5) integrating diverse datasets
trial: D1 + P1 → Rx
preclinical: D1+P1 → Rx
clinical: D2 + P1 → Rx
clinical: D1 + P2 → Rx
6) other pressures on preclinical
Strategy 3: Open Platform

- 5 active treatment arms and a control arm
- Pairwise independent analyses, treatment vs. control
- Frequent interim analyses
- Ineffective treatments are replaced with new treatments until significant comparison is found
Malaney et al Cancer Lett 2014
preclinical trials patients
ApoE-Directed Therapeutics Rapidly Clear β-Amyloid and Reverse Deficits in AD Mouse Models

Paige E. Cramer¹, John R. Cirrito², Daniel W. Wesson¹,³, C. Y. Daniel Lee¹, J. Colleen Karlo¹, Adriana E. Zinn¹, Brad T. Casali¹, Jessica L. Restivo², Whitney D. Goebel², Michael J. James⁴, Kurt R. Brunden⁴, Donald A. Wilson³, Gary E. Landreth¹,*
Multicenter Feasibility Study of Tumor Molecular Profiling to Inform Therapeutic Decisions in Advanced Pediatric Solid Tumors
The Individualized Cancer Therapy (iCat) Study
preclinical evidence, or "expert consensus"

<table>
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<th>Outcome of specimen profiling and expert panel review</th>
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<td>No iCat recommendation made</td>
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<td>[23-41]</td>
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<td>Technical failure/inadequate specimen</td>
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<td><strong>Total</strong></td>
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</tbody>
</table>
"based on preclinical data...in Nature... we offered this patient sorafenib + cetuximab"
2: threats to valid clinical generalization
design
noise

response

treatment

confound

local effect
i) internal validity
confound

animal

cause ➔ effect
sample size justification  0%
blinding  0%
randomization  37%
ii) construct validity
juvenile 75%
female 90%
immunosuppressed 81%

Mattina et al eLife 2015
iii) external validity
animal
cause → effect

human
cause → effect
a) incomplete methods
b) incomplete reporting
$1/\text{var}$ vs effect size
Design and Reporting of Targeted Anticancer Preclinical Studies: A Meta-Analysis of Animal Studies Investigating Sorafenib Antitumor Efficacy

James Mattina¹, Nathalie MacKinnon¹, Valerie C. Henderson¹, Dean Fergusson², Jonathan Kimmelman¹
3: the inferential threat
Reproducibility Project: Cancer Biology

Investigating reproducibility in preclinical cancer research.

COLLECTION Dec 10, 2014
BET Bromodomain Inhibition as a Therapeutic Strategy to Target c-Myc
REPRODUCIBILITY PROJECT
Cancer Biology

will it reproduce?

- significance
- effect size
<p>| | |</p>
<table>
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<tr>
<td>trainees</td>
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</table>
SIGNIFICANCE
EFFECT SIZE
META-RESEARCH ARTICLE

Can cancer researchers accurately judge whether preclinical reports will reproduce?

Daniel Benjamin¹, David R. Mandel², Jonathan Kimmelman¹*

¹ Biomedical Ethics Unit/STREAM, McGill University, Montreal, Canada, ² York University, Department of Psychology, Toronto, Canada
Danny Benjamin, PhD
4: proposals
1) clinical grade evidence
confirmatory preclinical studies
confirmatory

- powered
- blinded, etc.
- prespecified
- prosp. registered
2) better study reporting
75% licensed

37% ‘stalled’
3) clinical grade inference
(805/1474). Of these patients, only 45% (362/805) had an alteration ranked as levels 1–3 to support this claim, suggesting that physicians may have a less stringent definition of actionability than expert curators (Figure 2). Further evaluation of patients for targeted therapy and other actionable alterations is needed.
1) Decision-maker
   - content training
   - cognitive training
   - feedback
1) Decision-maker
- content training
- cognitive training
- feedback

2) Machine
- user interfaces
- better evidence
- less noise
4: story of imatinib
1) what fraction of trajectories lead to clinically actionable evidence?

1) when do trajectories lead to clinically actionable evidence?
Imatinib
- First approval-seeking
- Label-extending

Dasatinib
- First approval-seeking
- Label-extending

Nilotinib
- First approval-seeking
- Label-extending

= 100 patients
Non-precision medicine trials

Precision medicine trials

All drugs

= 100 patients