

Responsible Research and Innovation

A workshop

Ulf Toelch
Emma Pietsch
Sophia Rotter

Goals and Program

Reflection on current research practices and next steps

Schedule:

20 Minutes Introduction

1 hour: 2 Breakout Groups:

Group 1 (recommended for ECRs and interested PIs): Transparency and challenges

Group 2 Challenges in Translation in PM

20 Mins Wrap-up with the group

Responsible Research and Innovation is

“a transparent, interactive process by which societal actors and innovators become mutually responsive to each other with a view to the (ethical) acceptability, sustainability and societal desirability of the innovation process and its marketable products (in order to allow a proper embedding of scientific and technological advances in our society)” (Von Schomberg 2012, p. 9)

Responsible conduct of research (RCR)

promotes the production of *robust knowledge*, can be used to foster a healthy research culture, and ultimately will lead to the *public's trust* in the research process, its output, and its implementation.

What does this mean for Personalised Medicine?

Clinical Validity

is the likelihood by which
a test or algorithm identifies a patient's clinical status

Clinical Utility

is the benefits and harms that result from the
use of the test

Critical appraisal of existing genetic risk factors



Marcus Munafò

@MarcusMunafò

Folgen



Decades of early research on the genetics of depression were built on nonexistent foundations. How did that happen?

[theatlantic.com/science/archiv ...](https://www.theatlantic.com/science/archive/2019/05/waste-1000-studies/589684/) by @edyong209



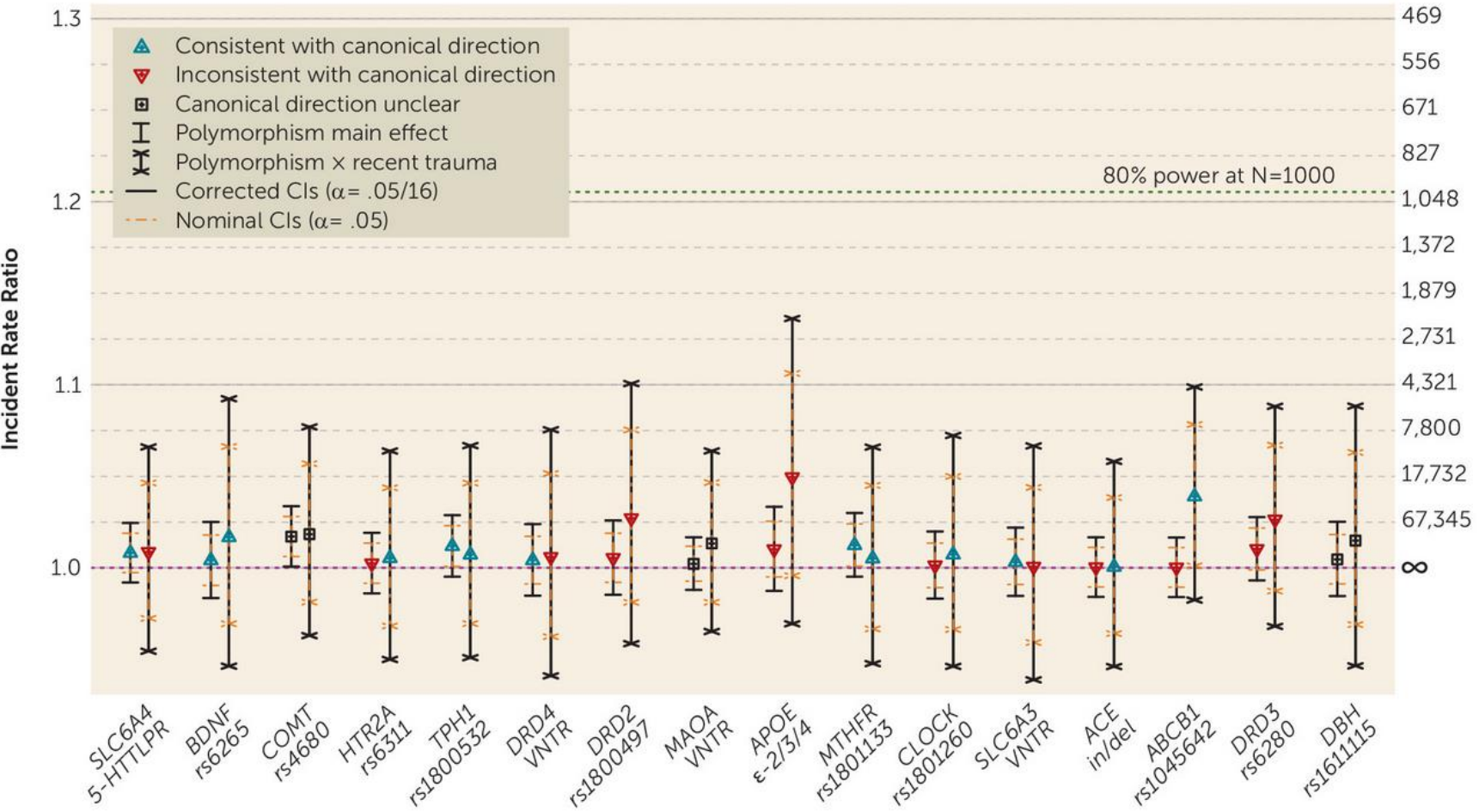
A Waste of 1,000 Research Papers

Decades of early research on the genetics of depression were built on nonexistent foundations. How did that happen?

<https://www.theatlantic.com/science/archive/2019/05/waste-1000-studies/589684/>


Researchers studied how SLC6A4 affects emotion centers in the brain, how its influence varies in different countries and demographics, and how it interacts with other genes. It's as if they'd been "describing the life cycle of unicorns, what unicorns eat, all the different subspecies of unicorn, which cuts of unicorn meat are tastiest, and a blow-by-blow account of a wrestling match between unicorns and Bigfoot"

B. Current Depression Severity



FULL ACCESS | Articles | Published Online: 8 March 2019

No Support for Historical Candidate Gene or Candidate Gene-by-Interaction Hypotheses for Major Depression Across Multiple Large Samples

Richard Border, M.A. , Emma C. Johnson, Ph.D., Luke M. Evans, Ph.D., Andrew Smolen, Ph.D., Noah Berley, Patrick F. Sullivan, M.D., and Matthew C. Keller, Ph.D. [AUTHORS INFO & AFFILIATIONS](#)

Publication: American Journal of Psychiatry • Volume 176, Number 5 • <https://doi.org/10.1176/appi.ajp.2018.18070881>

Genetic risk factors in complex diseases

Article

Mapping genomic loci implicates genes and synaptic biology in schizophrenia

Largest genome-wide association study

<https://doi.org/10.1038/s41586-022-04434-5>

Schizophrenia has a heritability of 60–80%¹, much of which is attributable to common risk alleles. Here, in a two-stage genome-wide association study of up to 76,755

Genes prioritized from common variant analyses are enriched in rare variant risk

Article

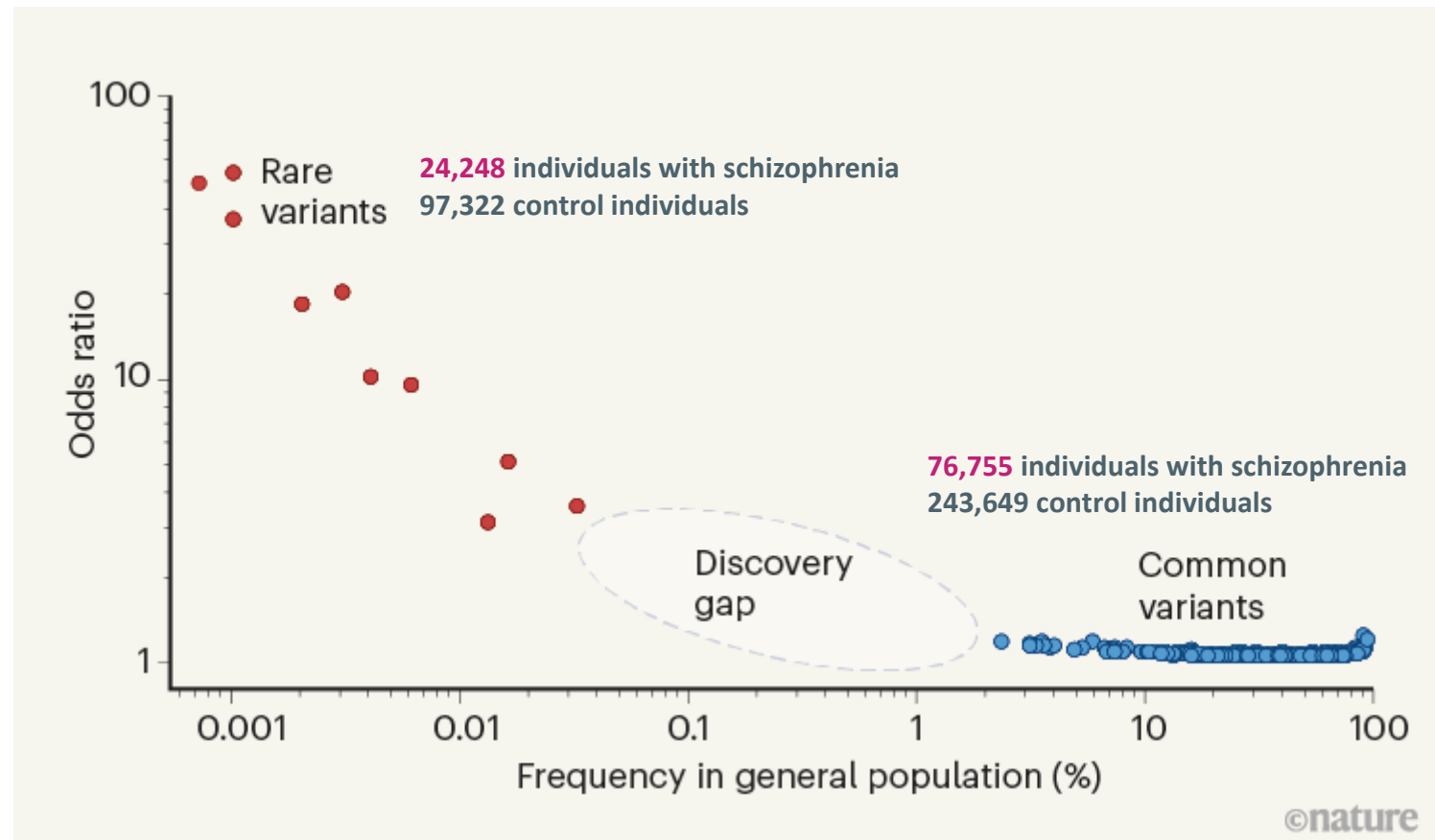
Rare coding variants in ten genes confer substantial risk for schizophrenia

Identified genes have the greatest expression in central nervous system neurons, diverse molecular functions including formation, structure and function of the synapse

<https://doi.org/10.1038/s41586-022-04556-w>

Rare coding variation has historically provided the most direct connections between

Common and rare genetic risk factors converge at least partially on the same underlying pathogenic biological processes



Nature **604**, 433-435 (2022)

<https://doi.org/10.1038/d41586-022-00773-5>

Single genetic mechanism often not sufficient to explain patient outcomes (ERCC1)

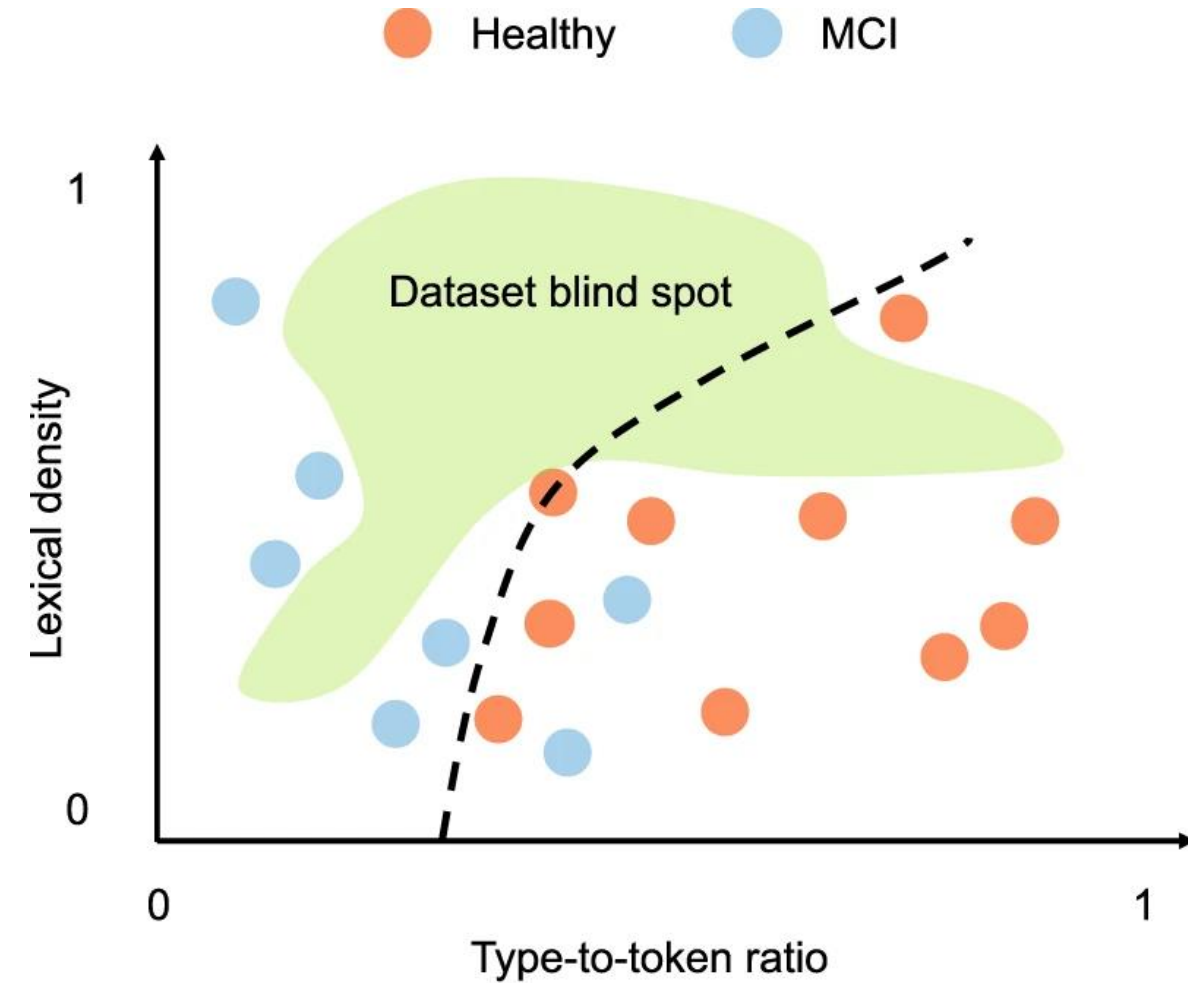
Accumulating Evidence and Research Organization graph stratified by biomarker ensemble, as defined by assay, tissue type, reagents, prespecified cutoff value, and drug regimen. Square nodes are retrospective analyses, and circular nodes are prospective trials.

->Ambiguous evidence for excision repair cross-complement group 1 (ERCC1)

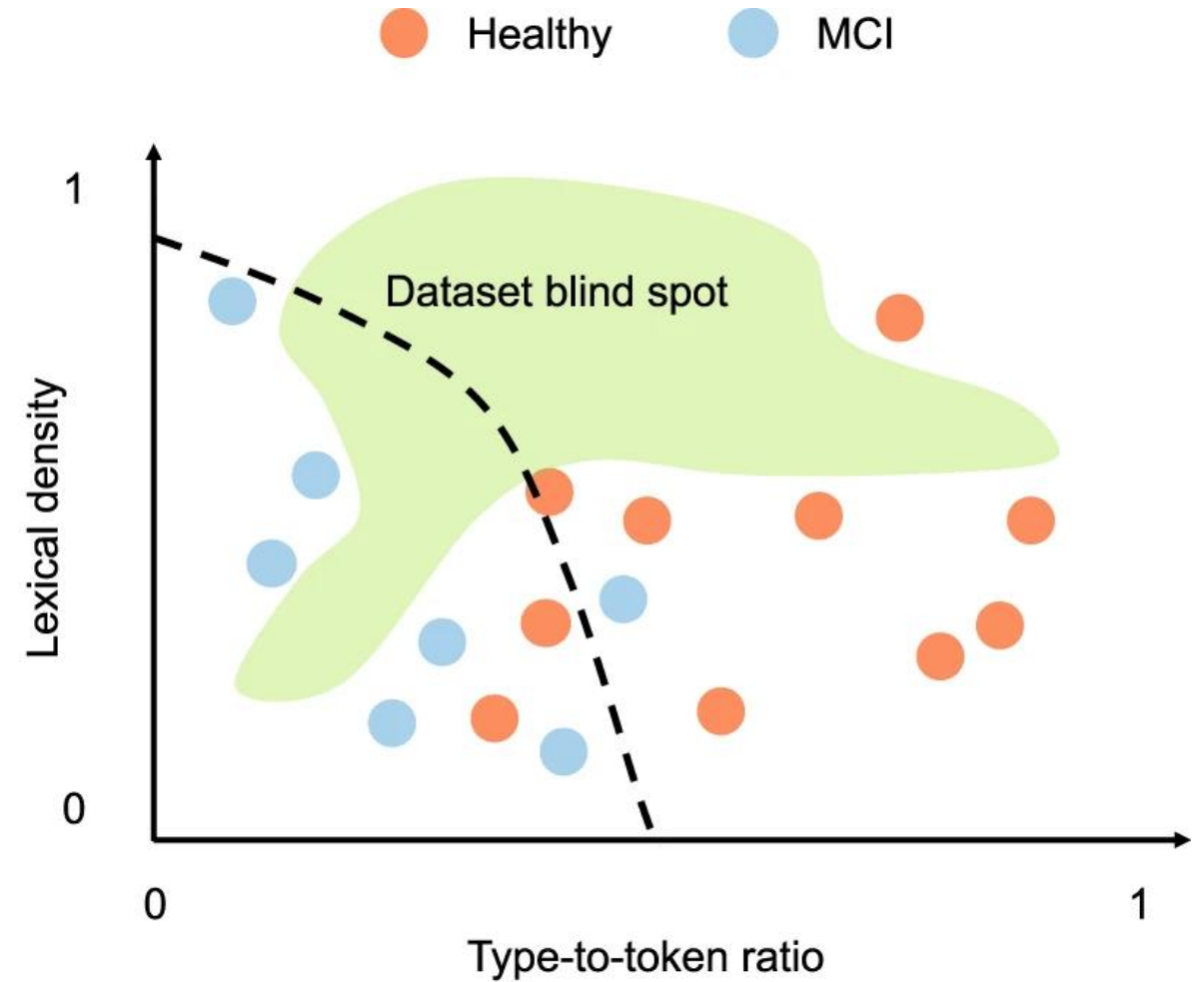


Barsanti-Innes, B., Hey, S. P., & Kimmelman, J. (2017). The Challenges of Validating in Precision Medicine: The Case of Excision Repair Cross-Complement Group 1 Diagnostic Testing. *The Oncologist*, 22(1), 89–96. <https://doi.org/10.1634/theoncologist.2016-0188>

Omics and the curse of dimensionality

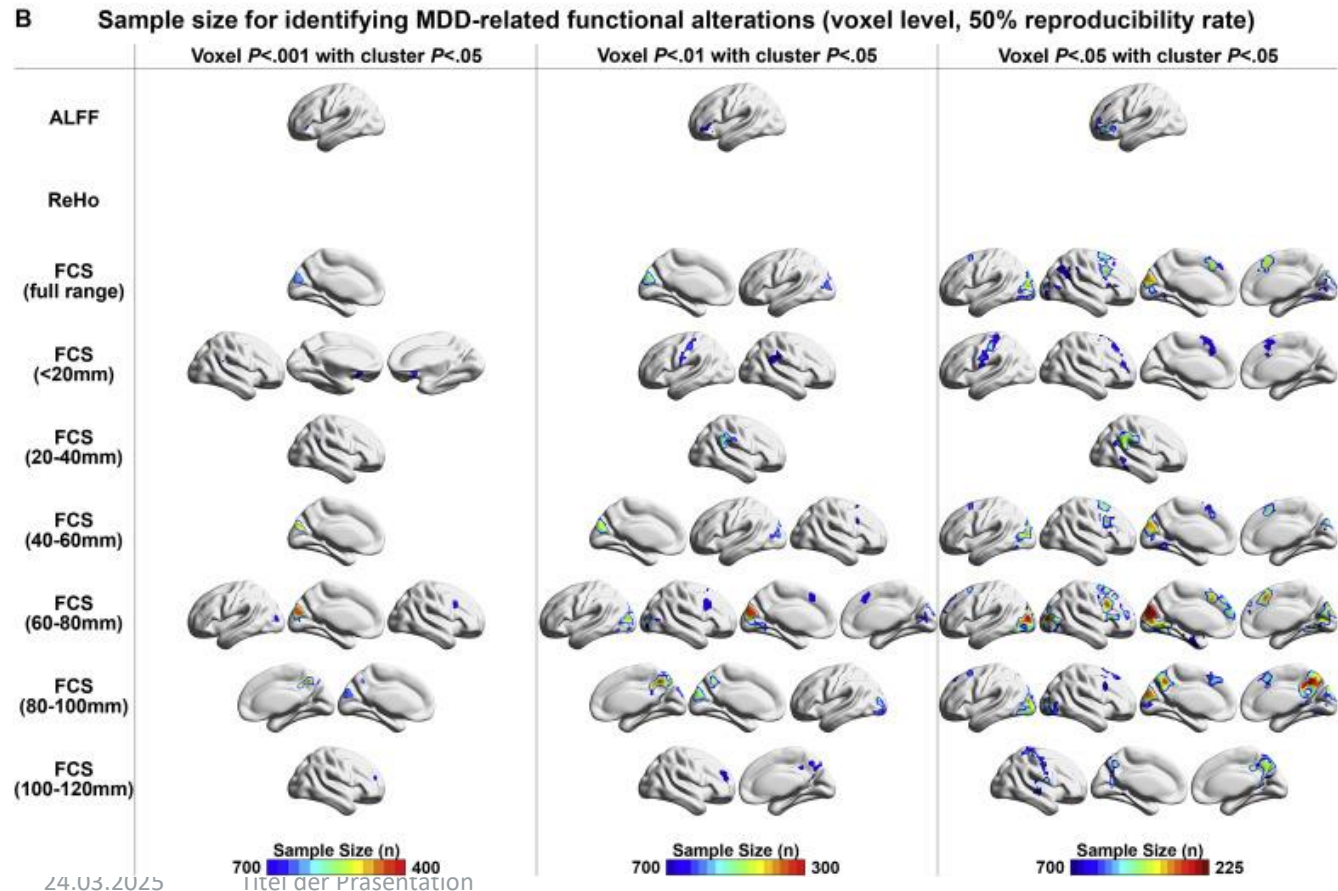
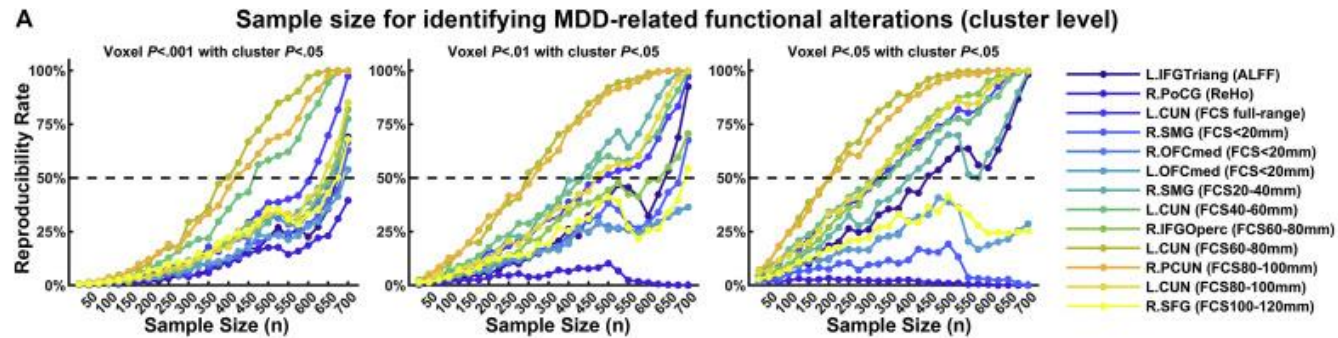


(a)



(b)

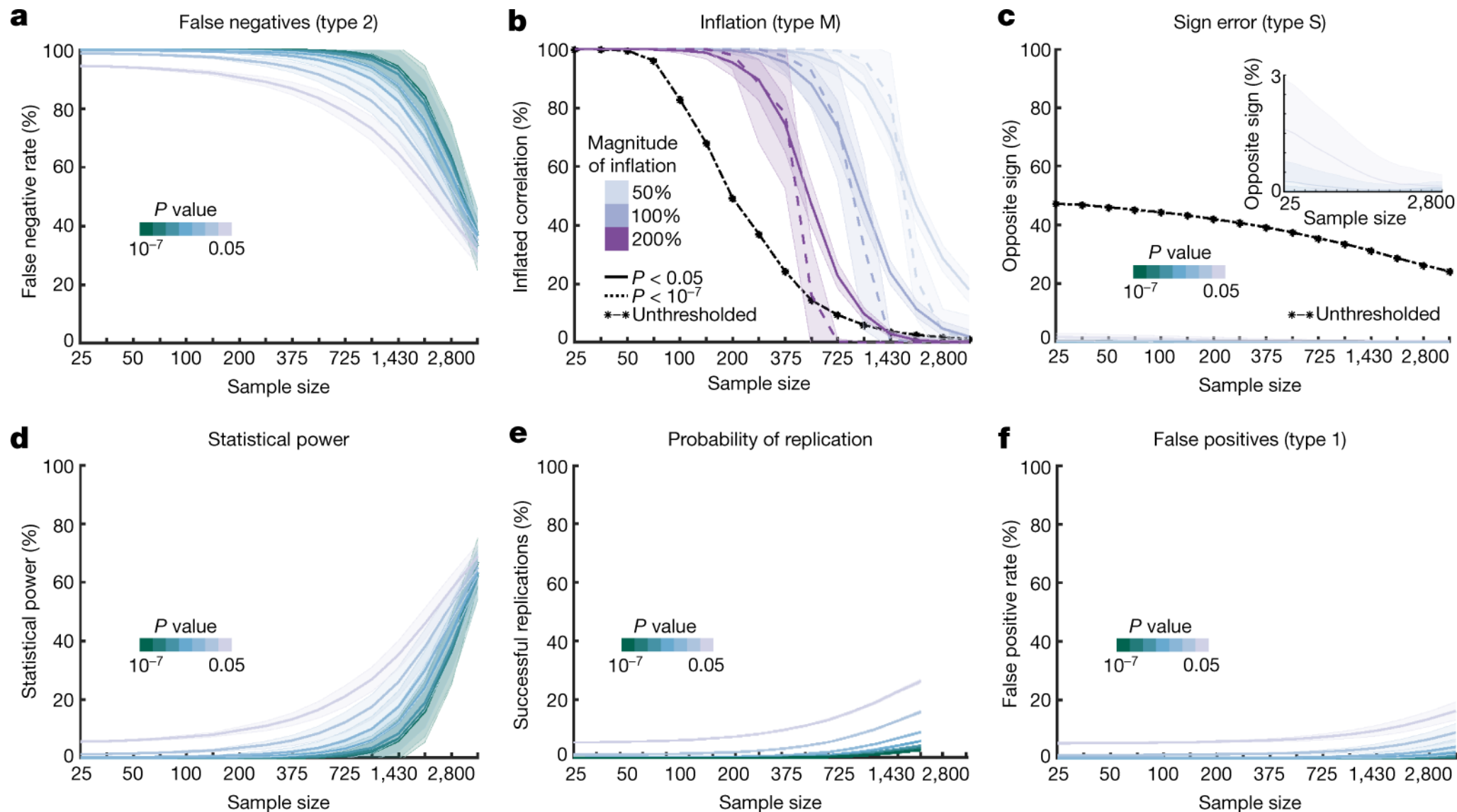
Resting state and Reproducibility in MDD



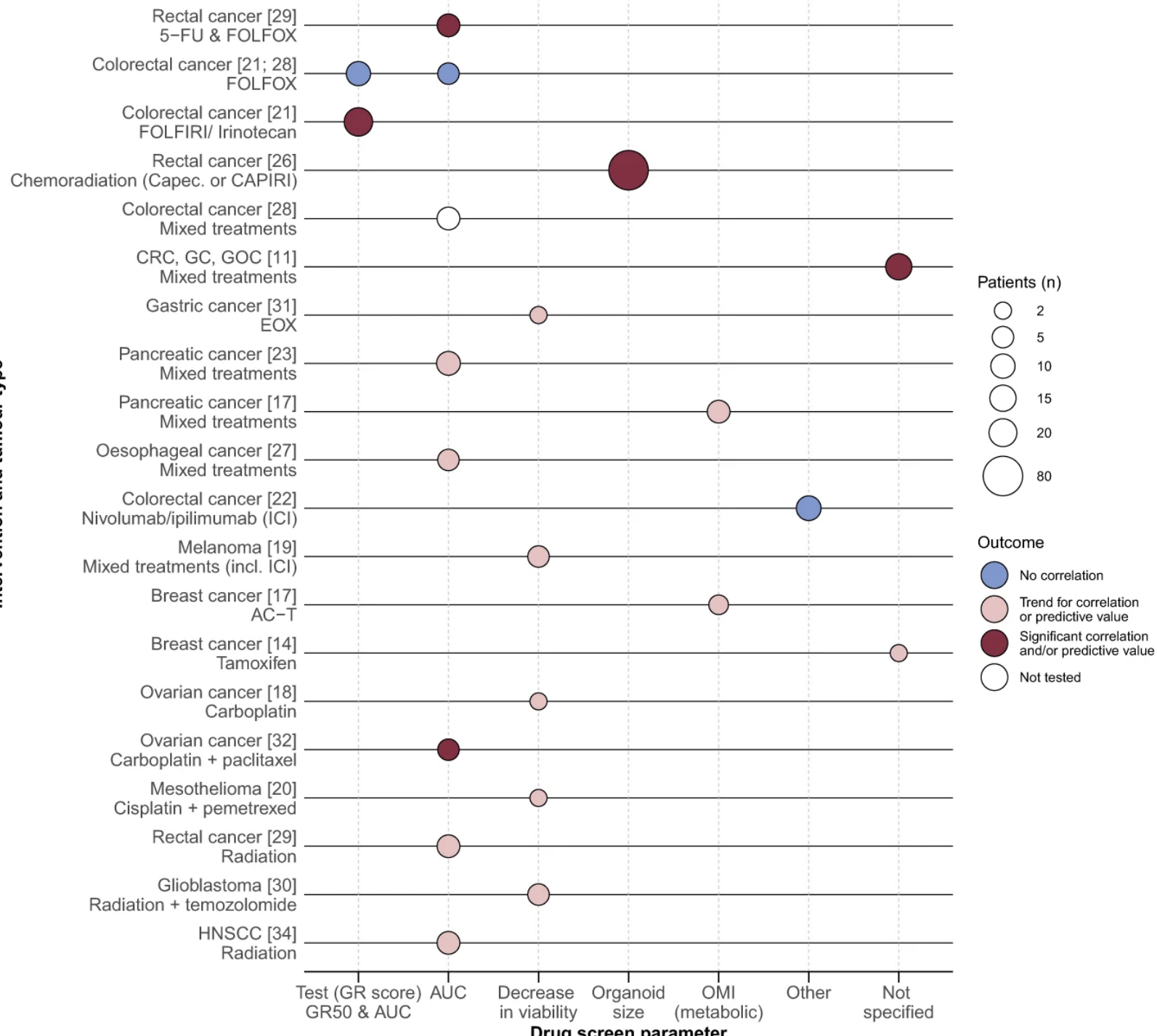
Xia, M., Si, T., Sun, X., Ma, Q., Liu, B., Wang, L., Meng, J., Chang, M., Huang, X., Chen, Z., Tang, Y., Xu, K., Gong, Q., Wang, F., Qiu, J., Xie, P., Li, L., & He, Y. (2019). Reproducibility of functional brain alterations in major depressive disorder: Evidence from a multisite resting-state functional MRI study with 1,434 individuals. *NeuroImage*, 189, 700–714.

<https://doi.org/10.1016/j.neuroimage.2019.01.074>

Also true for BWAS ... (n=3928 studies)



Marek, S., Tervo-Clemmens, B., Calabro, F.J. *et al.* Reproducible brain-wide association studies require thousands of individuals. *Nature* **603**, 654–660 (2022).
<https://doi.org/10.1038/s41586-022-04492-9>



Wensink, G.E., Elias, S.G., Mullenders, J. *et al.* Patient-derived organoids as a predictive biomarker for treatment response in cancer patients. *npj Precis. Onc.* 5, 30 (2021).
<https://doi.org/10.1038/s41698-021-00168-1>

Challenge	Recommendation
Moving beyond genomics	<ul style="list-style-type: none"> • Communicate and educate on the pros and cons of other omics technologies such as proteomics, metabolomics and lipidomics • Develop multi-modal data integration models that showcase the added value of multi-omics approaches in Personalized Medicine
New technologies, new challenges	<ul style="list-style-type: none"> • Share lessons-learned, failures and successes when evaluating new technologies in Personalized Medicine • Evaluate the added value of Artificial Intelligence and Digital health in Personalized Medicine, particularly in combination with multi-omics data
Data standardisation	<ul style="list-style-type: none"> • Adopt international standards of health data and models including the FAIR principles of data stewardship (e.g., OMOP, FHIR, CDISC) • Define criteria for quantity, quality and FAIR levels of data prior to multi-modal data analyses for a specific objective in Personalized Medicine • Work with flexible and dynamic mathematical models to adapt to changing data collections in Personalized Medicine
Variability in omics data at source	<ul style="list-style-type: none"> • Use internationally recognised laboratory standards and standard operating procedures for omics analyses • Adopt and apply quality assurance and control schemes for laboratories, such as the EATRIS Certificate of Commitment to Quality • Include confounding factors such as population diversity in biological systems in the multi-modal data analysis
Data privacy and regulatory aspects	<ul style="list-style-type: none"> • Consider ethical, legal, societal aspects when designing multi-omics Personalized Medicine studies • Comply with international standards on data security, including the General Data Protection Regulation in personal data • Report of the successes and failures of implementations from the European landscape
Implementation of Personalized Medicine in routine clinical care	<ul style="list-style-type: none"> • Consider well prior to multi-omics Personalized Medicine implementation: 1) the benefits, 2) the risks, 3) associated ethical and social aspects, 4) room for innovation

Clinical Validity

is the likelihood by which
a test or algorithm identifies a patient's clinical status

Clinical Utility

is the benefits and harms that result from the
use of the test

Research

Clinical value of guideline recommended molecular targets and genome targeted cancer therapies: cross sectional study

BMJ 2024 ; 386 doi: <https://doi.org/10.1136/bmj-2023-079126> (Published 20 August 2024)

Cite this as: BMJ 2024;386:e079126

[Article](#)[Related content](#)[Metrics](#)[Responses](#)[Peer review](#)

Ariadna Tibau , senior lecturer^{1 2}, Thomas J Hwang, initiative director^{1 3 4}, Jerry Avorn, professor¹, Aaron S Kesselheim, professor¹

Conclusion According to the ESCAT and ESMO-MCBS frameworks, about one eighth of genome based treatments for solid cancer were rated as likely to offer a high benefit to patients, whereas around a third were identified as offering a promising but unproven substantial benefit. Ensuring that NCCN recommendations are aligned with expected clinical benefits is crucial for promoting informed, evidence based, genomic guided treatment decisions.

> [JAMA Oncol.](#) 2024 May 1;10(5):634-641. doi: 10.1001/jamaoncol.2024.0194.

Clinical Value of Molecular Targets and FDA-Approved Genome-Targeted Cancer Therapies

[Ariadna Tibau](#)^{1 2}, [Thomas J Hwang](#)^{1 3 4}, [Consolacion Molto](#)⁵, [Jerry Avorn](#)¹,
[Aaron S Kesselheim](#)¹

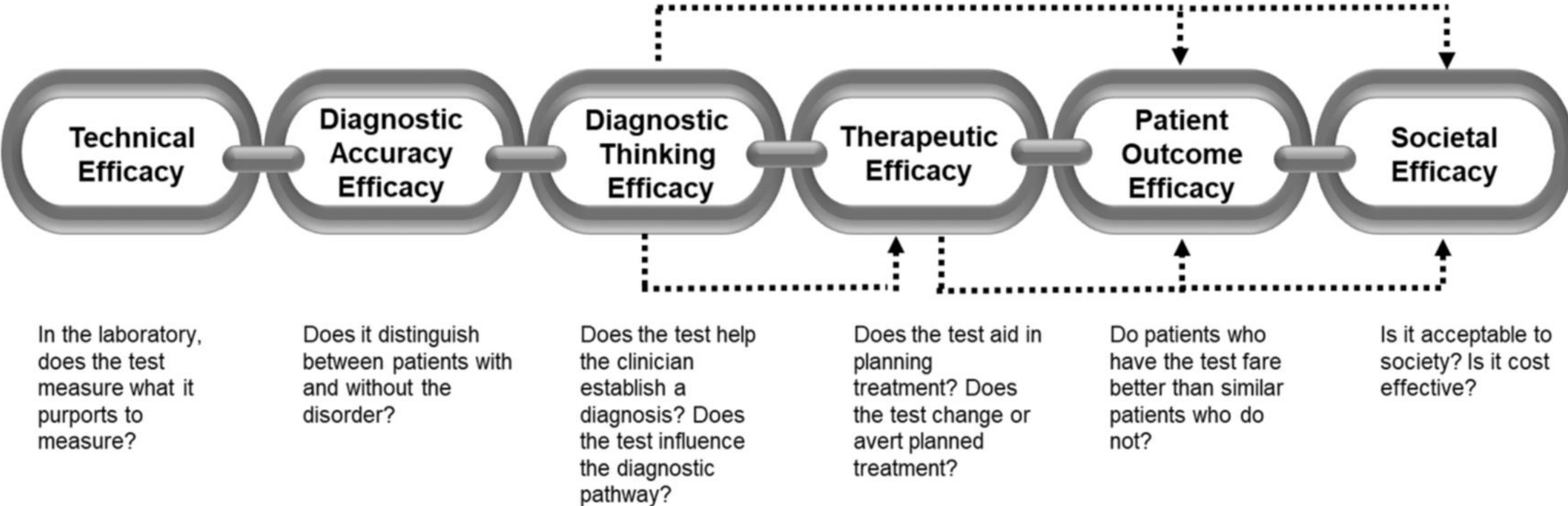
Affiliations + expand

PMID: 38573645 PMCID: PMC11099684 (available on 2025-04-04)

DOI: [10.1001/jamaoncol.2024.0194](#)

Conclusions and relevance: The results of this cohort study demonstrate that among recently approved molecular-targeted cancer therapies, fewer than one-third demonstrated substantial patient benefits at approval. Benefit frameworks such as ESMO-MCBS and ESCAT can help physicians, patients, and payers identify therapies with the greatest clinical potential.

Clinical utility as chain of efficacy



..... Plausible relationships among links in the chain of evidence

Hayeems, R. Z., Dimmock, D., Bick, D., Belmont, J. W., Green, R. C., Lanpher, B., Jobanputra, V., Mendoza, R., Kulkarni, S., Grove, M. E., Taylor, S. L., & Ashley, E. (2020). Clinical utility of genomic sequencing: A measurement toolkit. *Npj Genomic Medicine*, 5(1), 1–11. <https://doi.org/10.1038/s41525-020-00164-7>

Splitting the groups 60 mins

Group 1 (Emma/Sophia): Transparency and ECR specific challenges

Recommended for ECRs and interested PIs

Group 2 (Ulf): Clinical validity and utility

Recommended for PIs

Clinical Validity likelihood by which a test or algorithm identifies a patient's clinical status

Moving beyond genomics. What opportunity/challenges do you see? What factors do you or would you like to consider beyond genomics? How to integrate multimodal data?

How do you communicate/learn about success/failures in new technologies in PM?

How standardized are data collection / curation processes? How interoperable are data sets?

How large/diverse are your study populations? How generalizable are your results?

Do you validate with external data sets?

Clinical Utility is the benefits and harms that result from the use of the test

Are you using a utility framework? Which one are you using?

What are main opportunities/challenges to bring your insights to patients?

What do you consider a successful transfer/translation? How do your interventions compare to standard of care?

Thank you.