PIP Digest

Canadian Cancer Research Alliance
Alliance canadienne pour la recherche sur le cancer

Patient Involvement in Cancer Research Program
Programme de Participation des Patients à la recherche sur le cancer

CANCER RESEARCH: Research Quality

This PIP Digest looks at the important issue of research quality and continuing efforts to reduce bias in research studies.

Key Concepts

- Components of research quality
- Impact of bias on research

Related PIP Digests

- Research Studies: Assessing Evidence
- Research Studies: Understanding Research Articles

High-quality, trustworthy research is the foundation of every advance in cancer detection, prevention, and treatment. While some people's trust might be shaken by recent high-profile fraud cases, where renowned cancer researchers have been accused of falsifying data, academic institutions, publishers, research funders, and governments have all renewed their efforts to reinforce the three cornerstones of research quality: **rigor, reproducibility, and transparency**.

Rigor

Rigor comes from designing experiments and studies whose methodology, analysis, and interpretation and reporting of results are robust and unbiased. Robust studies incorporate adequate controls and appropriate measures, sound data preparation and management, clear, testable hypotheses, and other scientific best practices.

Guarding against bias presents complex, multi-faceted challenges. Bias can take many forms. One of the most pervasive is confirmation bias. Confirmation bias occurs when a researcher (wittingly or unwittingly) designs a study whose results are destined to confirm, rather than test, a belief or hypothesis.

One troubling example of confirmation bias was the advocacy for ultra-radical breast cancer surgery in the 1950s and 1960s, which is described by Siddahartha Mukherjee in his chronicle of the history of cancer.[1] The surgeons that Mukherjee describes were so convinced of their hypothesis — namely that preemptive, highly extensive surgery could rid the body of cancer — that for years they prevented clinical trials that would test whether less invasive approaches could achieve comparable or better results from being conducted in the United States. As a result, many patients underwent major, unnecessary surgeries and suffered serious complications and long-term effects without reduced risk of mortality.

[1]Mukherjee, S. (2010). *The Emperor of All Maladies: A Biography of Cancer*. New York: Scribner.

More recently, there has been a push to "triangulate" study results.[2] This means explicitly acknowledging sources of bias and conducting research using multiple experimental approaches to correct and control for different kinds of bias.

Reproducibility

A **reproducible** study can have its results reproduced by an independent researcher using the same study design, methodology, and analysis. If a study can't be reproduced, it indicates a problem with the original research. Conducting studies that are reproducible means doing research with the best available models and human tissues and samples (biospecimens).[3]

Hugely important activities include:

- developing animal models that can better predict human response
- standardizing policies and guidelines for isolating, processing, analyzing, and characterizing human biospecimens
- linking the data on biospecimens to patient outcomes and other information (called clinical annotation)

In the past decade, cancer researchers have had to respond to a "reproducibility crisis" that has disrupted many areas of health research. The "Reproducibility Project: Cancer Biology" initiative independently replicates selected results from high-profile papers in the field of cancer biology. For each paper, a Registered Report detailing the proposed experimental designs and protocols for the replications is peer reviewed and published prior to data collection. The results of these experiments are then published as a Replication Study. This project is a collaboration between the Center for Open Science and Science Exchange. For more information, see https://cos.io/rpcb/.

Several academic journals now offer reproducibility checklists to help promote more rigorous science. And a global initiative called EQUATOR (Enhancing the QUAlity and Transparency Of health Research) is the systematically tackling issues around reliability and reproducibility in published health research. This project promotes transparent and accurate reporting and wider use of robust reporting guidelines. EQUATOR provides checklists for all types of research studies. For more, see http://www.equator-network.org.

Transparency

Transparency refers to the level of detail researchers offer publicly with their research results. In a perfectly transparent world, all researchers would provide unrestricted, free-of-charge access to their raw data, including details on sample size calculations, information on how data were excluded or manipulated, their data analysis scripts and/or code, and details on their measures and models. Greater transparency enables better, more meaningful assessments of reproducibility.

[2]Marcus R. Munafò and George Davey Smith. (2018). Robust research needs many lines of evidence. *Nature*, 553:399-401.

[3]Biemar, F. & Margaret Foti, M. (2013). Global progress against cancer—challenges and opportunities. *Cancer Biology & Medicine*, 10(4):183–6.

The “open-access journal movement” encourages greater access to research and data. Academic culture, though, is slow to change. Funding for research is fiercely competitive. Researchers face significant pressure to publish — even tentative and non-innovative — findings in the most prestigious journals, and to hype their work to attract more research dollars. Journals and non-peer-reviewed media also have a bias toward positive results and headline-grabbing advances. For complex challenges like cancer, high-quality science benefits most from a research culture that promotes and rewards team science, especially among cross-disciplinary, multi-institutional teams — which also happen to reduce bias!

PLOS ONE, started in 2007, was the world’s first multidisciplinary open-access journal. It continues to drive cultural change around open-access science. The journal accepts all kinds of research, including replication studies and negative results, so long as the research is scientifically rigorous. For more, go to https://journals.plos.org/plosone/. If you are interested in more about this topic, the journal *Nature* has curated a series of articles looking at the challenges of reproducibility. They can be accessed at https://www.nature.com/collections/prbfkwmwvz.

Plan S is an initiative for Open Access publishing that was launched in September 2018. The plan is supported by cOAlition S, an international consortium of research funders. Plan S requires that scientific publications that result from research funded by public grants must be published in compliant Open Access journals or platforms starting in 2020. For more, see https://www.coalition-s.org/.

Negative Results have Positive Value

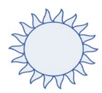
Experiments that go according to plan are obviously useful. But often the biggest scientific advances emerge from those that do not. The publication of negative findings, while often neglected or downplayed, provides vital information to the scientific community.

While serendipity can (very occasionally) play a role in science, solid interpretation of research findings almost always comes from a well-designed, well-controlled study and from scientists accepting and building on null findings and findings that contradict their original hypothesis.

Case Study

Cancer research progresses via forming, reforming, and refining hypotheses. But one of the most illuminating standalone examples of how this process works comes from research into the unrelated condition of multiple sclerosis (MS). Observational research from the 1970s showed that MS was much rarer among populations that lived near the equator. Some researchers hypothesized that Vitamin D — which our bodies produce from the sun, and therefore more abundant in warmer climates—might help prevent this disease of the central nervous system. Subsequent research did not support this hypothesis, but it did suggest that ultraviolet radiation from the sun might help prevent MS. Researchers designed a mouse study to test this hypothesis.

Mice injected with MS-causing chemicals were separated into four groups:

FOUR GROUPS		
exposed to the preventative UV [experimental group]	√	
exposed to the preventative UV + sunscreen [control group 1]	√	√
exposed to sunscreen [control group 2]		√
not exposed to sunscreen or UV [control group 3]		

This experiment did not support the hypothesis that exposure to UV would slow MS. In fact, it turned out that the mice that were protected from UV exposure with sunscreen had the slowest progression. Further research revealed that key compounds in the sunscreen inhibited the progression of MS. Although, the original hypothesis was wrong, the experiment opened new, promising lines of investigation into these chemicals.[4]

View these videos to expand your knowledge of research quality:

- Monya Baker. *Is there a reproducibility crisis?* (Nature) May 25, 2016 [2:03 minutes] https://www.nature.com/news/1-500-scientists-lift-the-lid-on-reproducibility-1.19970
- Elizabeth Iorns. *Prioritizing reproducibility for scientific advancement*. (TEDMED) June 16, 2015 [4:14 minutes] https://www.tedmed.com/talks/show?id=526199
- Matt Anticole. *Is there a reproducibility crisis in science?* (TED-Ed/YOUTUBE) December 5, 2016 [4:46 minutes] https://www.youtube.com/watch?v=FpCrY7x5nEE

Last revised: 2019-July-19

[4]Wang, Y. et al. (2017). Salate derivatives found in sunscreens block experimental autoimmune encephalomyelitis in mice. *Proceedings of the National Academy of Sciences*, 114(32):8528–31. [Original source: The Economist, July 29, 2017, p. 70.]