

Costs of Reproducibility Crisis

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Public Comments; Committee on Reproducibility and Replicability in Science

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Scientific Apophenia

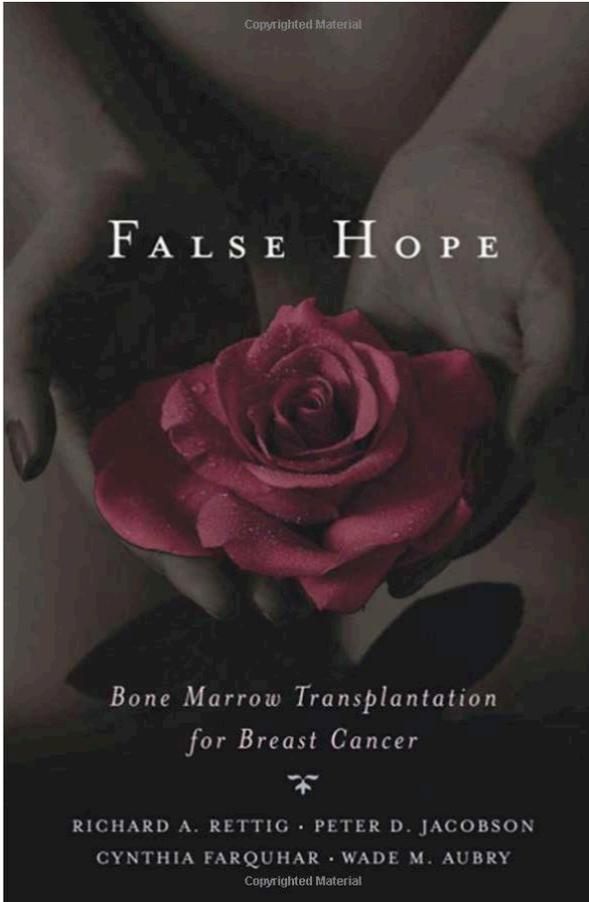
- Apophenia: *The human tendency to seek patterns in random information.* (<http://en.wikipedia.org/wiki/Apophenia>)
- Scientific Apophenia: *assigning of inferential meaning when limited statistical power should prevent such a conclusion or when the data are actually random.*

- Goldfarb & King, 2016

Breast Cancer & Bone Marrow Transplants (HDC/ABMT)

- Devastating and salient disease:
 - Young Women
 - Low survival (particularly Stages III and IV).
- Idea (1982):
 - Super-lethal doses of chemotherapy to aggressively target fast growing cancer cells.
 - Bone marrow transplants to replace destroyed marrow

Timeline of Narrative (HDC/ABMT)



- Increases treatment response at 3 years
- Early evidence based on archival interpretation of previous studies
- Not wrong, but speculative



Timeline: HDC/ABMT

\$60,000,000

Hryniuk & Bush (1984)
Hyrniuk & Levine (1986)
Endorsed by NCI Director

Ignored critique
Henderson et al. (1988)

Clinical Trials
(~1,000 women)
1988-2001

Clinical Treatment
(35,000 Women)
1988-2001

\$50,000

\$50,000

\$1,750,000,000

Application Costs: HDC/ABMT

Hryniuk
Hyrn

29X

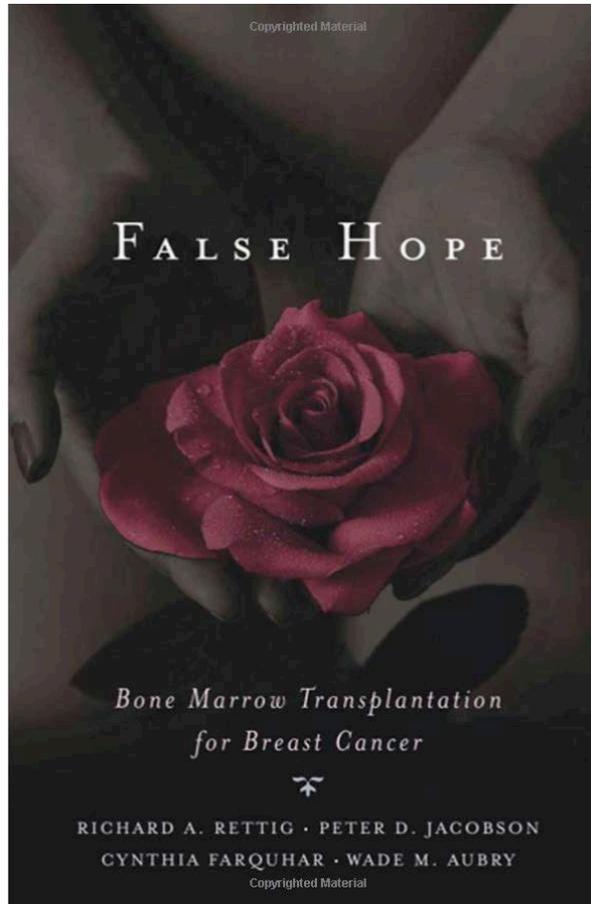
\$60,000,000

\$50,000

\$50,000

\$1,750,000,000

Timeline of Narrative



- ~ 40,000 patient underwent HDCT + BMT
 - Harder to recruit patients
 - ~600 died from treatment
- No survival increase at 5 years
- gastrointestinal toxicity, nausea, vomiting and diarrhea, infection and organ toxicity” - Howard et al. 2011

Error Cost Escalation (Software)

	Method 1 Cost Factors	Software Cost Factors
Requirements	1X	1X
Design	8X	5X – 7X
Build	16X	10X – 26X
Test	21X	50X – 177X
Operations	29X	100X – 1000X

Table 4: Comparison of Method 1 and Software Cost Factors

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Table 4: Comparison of Method 1 and Software Cost Factors

General Science

- Original Study
- Citing Studies
- Applications

Costs of Poor Reproducibility

- **Direct Costs**

- Costs of producing bad research

- ***We can be reasonably certain about these.***

- **House of Cards – Indirect Costs**

- **Science that builds on incorrect results**

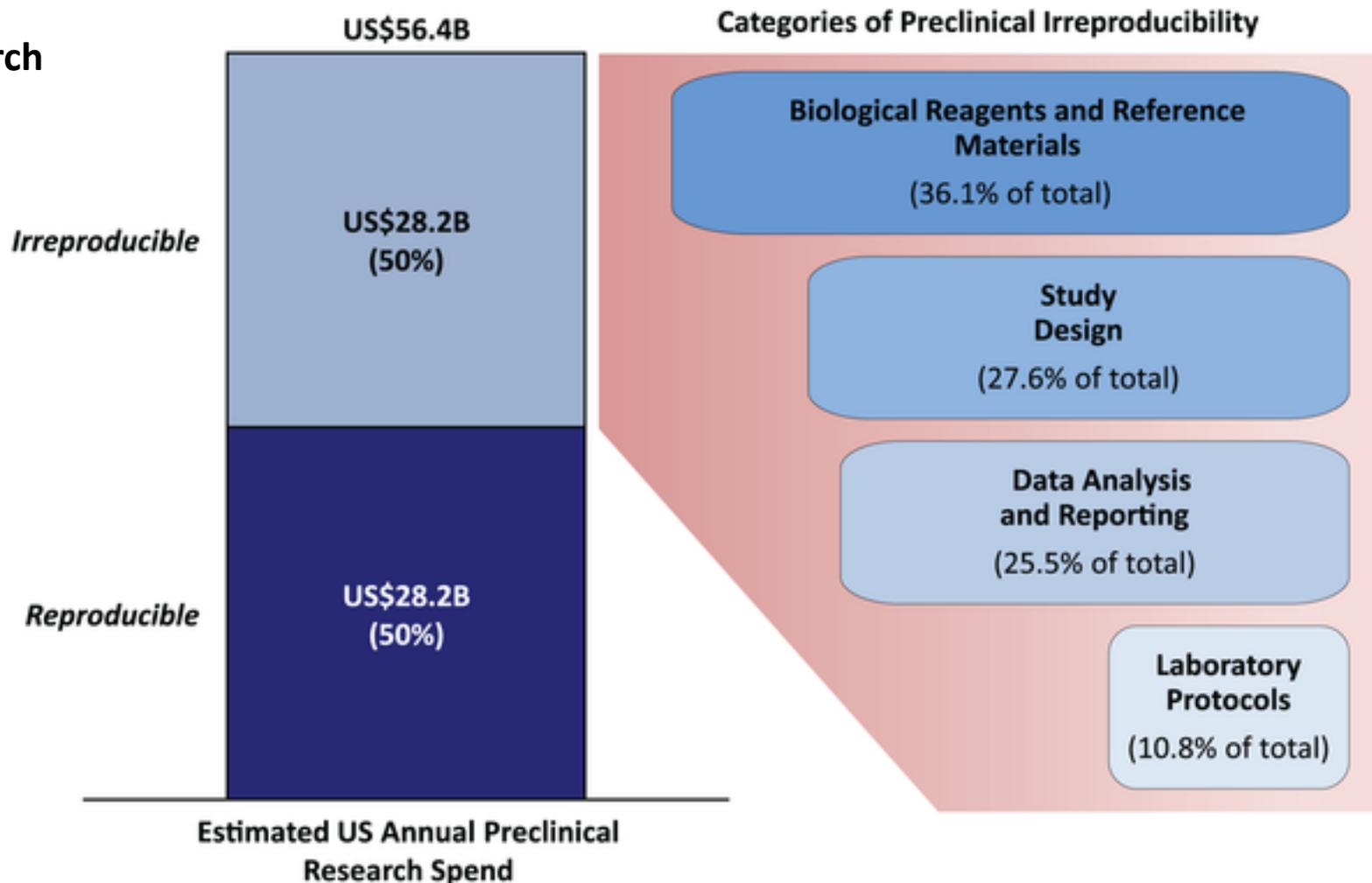
- Building on
- Striking down

- **Applications**

- ***Much harder to Guesstimate***

Fig 2. Estimated US preclinical research spend and categories of errors that contribute to irreproducibility.

Direct Costs
Pre-clinical bio research



Freedman LP, Cockburn IM, Simcoe TS (2015) The Economics of Reproducibility in Preclinical Research. PLOS Biology 13(6): e1002165.

<https://doi.org/10.1371/journal.pbio.1002165>

<http://journals.plos.org/plosbiology/article?id=10.1371/journal.pbio.1002165>

Examples of Harmful Applications

- HDC/ABMT
- Hormone Replacement Therapy for Menopausal Women
- Stents for Low Severity SCAD (Stable Coronary Arterial Disease)
 - ~\$ 3.5B annually (2002-2005; extrapolated from Greenwood et al., 2017)
- But most studies implications do not make it into practice.



Costs: Use Basic & Applied R&D Expenditures 2016 – \$180B

\$90B @ 50%



- Original Study

\$18B @ 20%



- Building on / Striking Down

\$13.5B – \$270B



- Applications to practice

We really don't know

- Rare events will have outsized effects on these estimates
- **Major assumptions drive numbers in the cost of misguided applications**
- **So... more research needed.**

Most policy is decided under uncertainty

- Decisions *must* be made with incomplete information
- What if HDC/ABMT had been effective?
 - Preliminary evidence was *inconclusive*.
 - *Breast cancer mortality has fallen substantially! (Mortality rate down 50% 1996-2006) (<https://www.prb.org/breastcancer/>).*
- No excuse for poor documentation
- Uncertainty gets lost in compelling “too good to be true” narratives.

Costs of remediation are small – from Center for Open Science – Brian Nosek

- Better Archives / Infrastructure – trivial, and mostly one time.
 - ~3,000,000 datasets posted!
 - Training of Research Community - \$750k Annually
 - Replications
 - Center for Open Science Estimate Approximately ~\$100K/study.

Recommendations

- Show your work / Share your outputs
- Open as default for all research outputs
- Much work to be done in establishing standards for disclosure
- Registration as the default as having been conducted.
 - Discovery oriented – register that it exists.

Sources / Further Reading

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Thank you!

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