Measuring Investigator Impact in Clinical Oncology with the Continuous Innovation Indicators™

Samuel Thomas
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Supported by Lilly Oncology

Health Research Alliance Members' Meeting
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Acknowledgements and Disclosures

- Thank you to HRA for the invitation
- This work was supported by Lilly Oncology's PACE (Patient Access to Cancer care Excellence) Initiative
- Key team members and collaborators include:
  - Silvia Paddock, Rose Li and Associates
  - Maneesh Kumar, Breast Cancer Research Foundation
  - Carole Wegner, V Foundation for Cancer Research

Goals

- Better understand one dimension of how grants from two foundations contribute to progress against cancer

- Assess how long it takes for basic research to measurably impact the treatment landscape

- Determine whether differences in long-term impact correlate with grant characteristics

- Use the results to inform strategic grant portfolio management

- Disseminate success stories to showcase impact

PACE Continuous Innovation Indicators (CII)

- Database and interactive tool that records, visualizes, and measures progress against 13 solid tumors

- Free for all to use for non-commercial purposes

- Includes evidence for increased overall survival from clinical trials, observational studies, and meta-analyses

- Shows that progress takes time and critically depends on basic research findings, follow-up studies, evaluation of combination therapies, and refinement of existing approaches
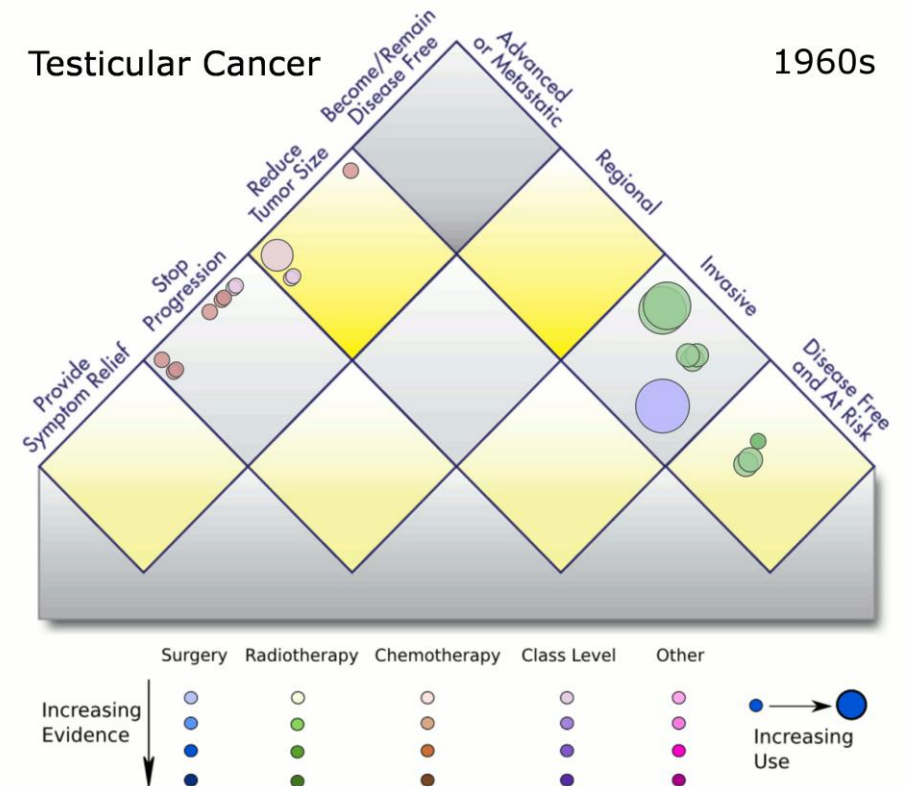

The PACE CII translates this **complex, dynamic process** into easy-to-understand visuals and quantitative scores. See http://scoringprogress.com

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Grant Programs Examined

- V Foundation for Cancer Research (VF)
  - 221 early career investigators funded between 1992-2010
  - Focus on all types of cancer, from basic to translational research

- Breast Cancer Research Foundation (BCRF)
  - 159 established investigators funded between 1992-2011
  - Focus on breast cancer only, from basic to clinical research

Methods – Linking Studies
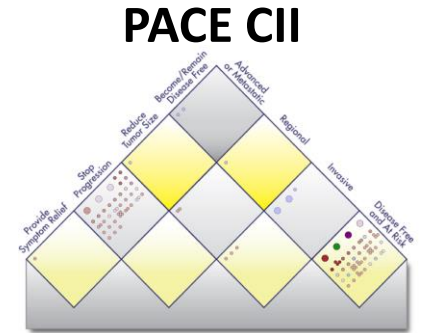
Grantees

Identify grantees
funded until
2010/11

PACE CII

Methods – Linking Studies
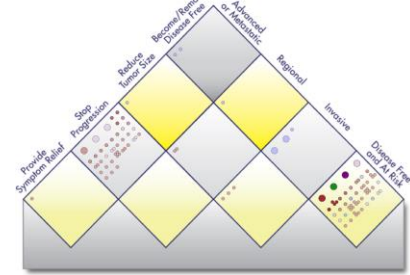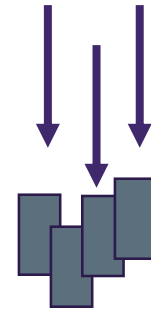
Grantees

Identify grantees funded until 2010/11

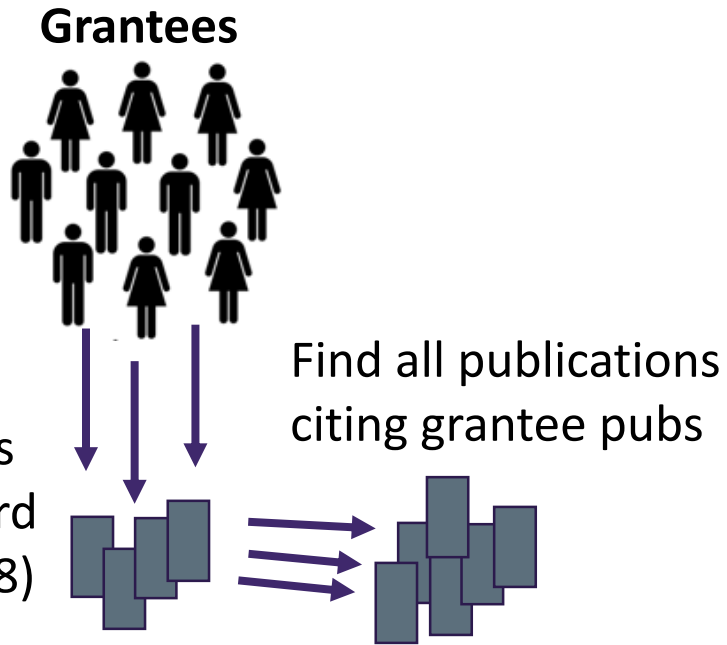Find all publications 5 years before award to present (2017/18)

PACE CII
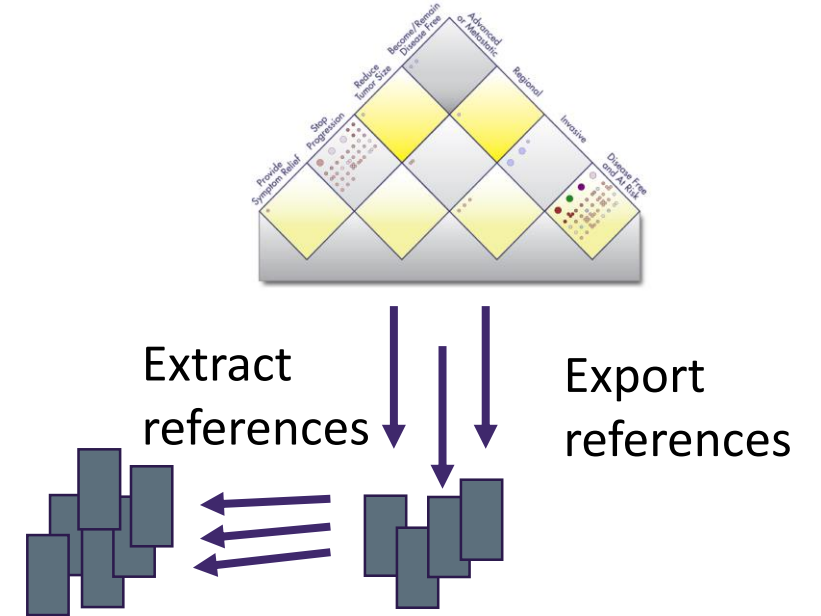
Export references

Methods – Linking Studies

Grantees

PACE CII

Identify grantees funded until 2010/11

Find all publications citing grantee pubs

Find all publications 5 years before award to present (2017/18)

Extract references

Export references

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Identify matches

First degree match

Diamonds indicate identical studies in the two datasets

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Methods – Linking Studies

Grantees

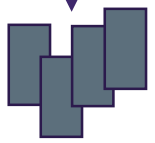**PACE CII**

Identify grantees funded until 2010/11

Find all publications 5 years before award to present (2017/18)

Find all publications citing grantee pubs

Extract references

Extract references

Export references

Identify matches

◆━━━━━━━━━━━━━━━◆ First degree match

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◆━━━━◆━━━━━━◆━━━◆ Second degree match

Methods – Linking Studies

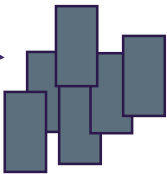**Grantees**

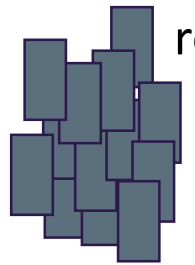**PACE CII**

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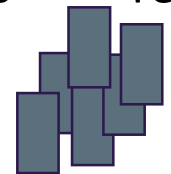
Find all publications 5 years before award to present (2017/18)

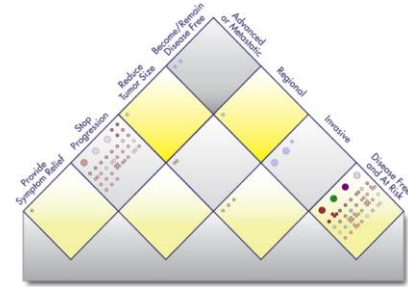Find all publications citing grantee pubs
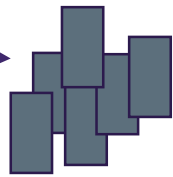
Extract references
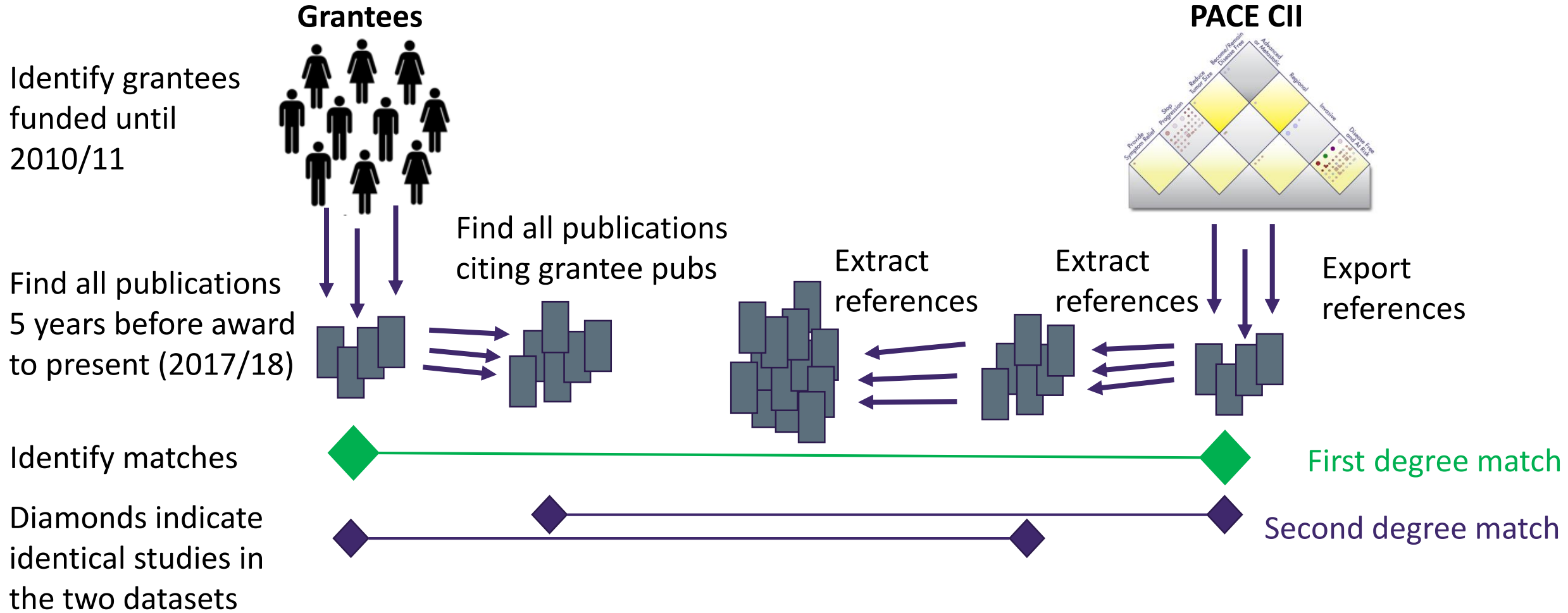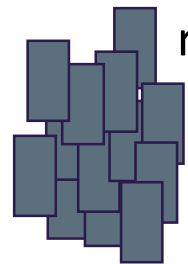
Extract references

Export references
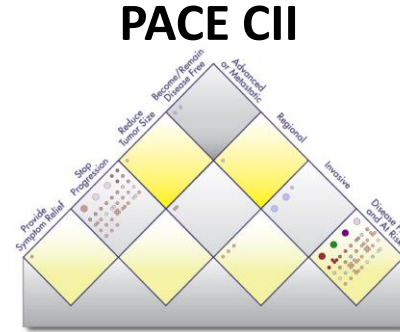
Identify matches

First degree match

Diamonds indicate identical studies in the two datasets

Second degree match

Third degree match

Fourth degree match

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Caveats

- We conducted the linkage using novel scripts connecting to the NCBI Entrez E-Utilities (https://www.ncbi.nlm.nih.gov/books/NBK25497/).

- We make no claims that this linkage comprehensive.

- Additional follow-up is necessary before drawing any conclusions about the productivity of individual researchers.

- Our approach cannot be used to make valid comparisons of impact between funding organizations.

V Foundation V Scholar Grants

- 207 early career investigators funded between 1992-2010
- Classified by V Foundation into four categories:

  B = biomarker or genomic signature

  C = cancer biology

  G = general cell biology

  T = treatment-related

- 14 out of 221 scholars excluded due to name disambiguation issues or evidence of abandoned grants.

VF Results: Number of Linkages

Number of Linked Scholars per Group

Number of Linked Publications Per Scholar
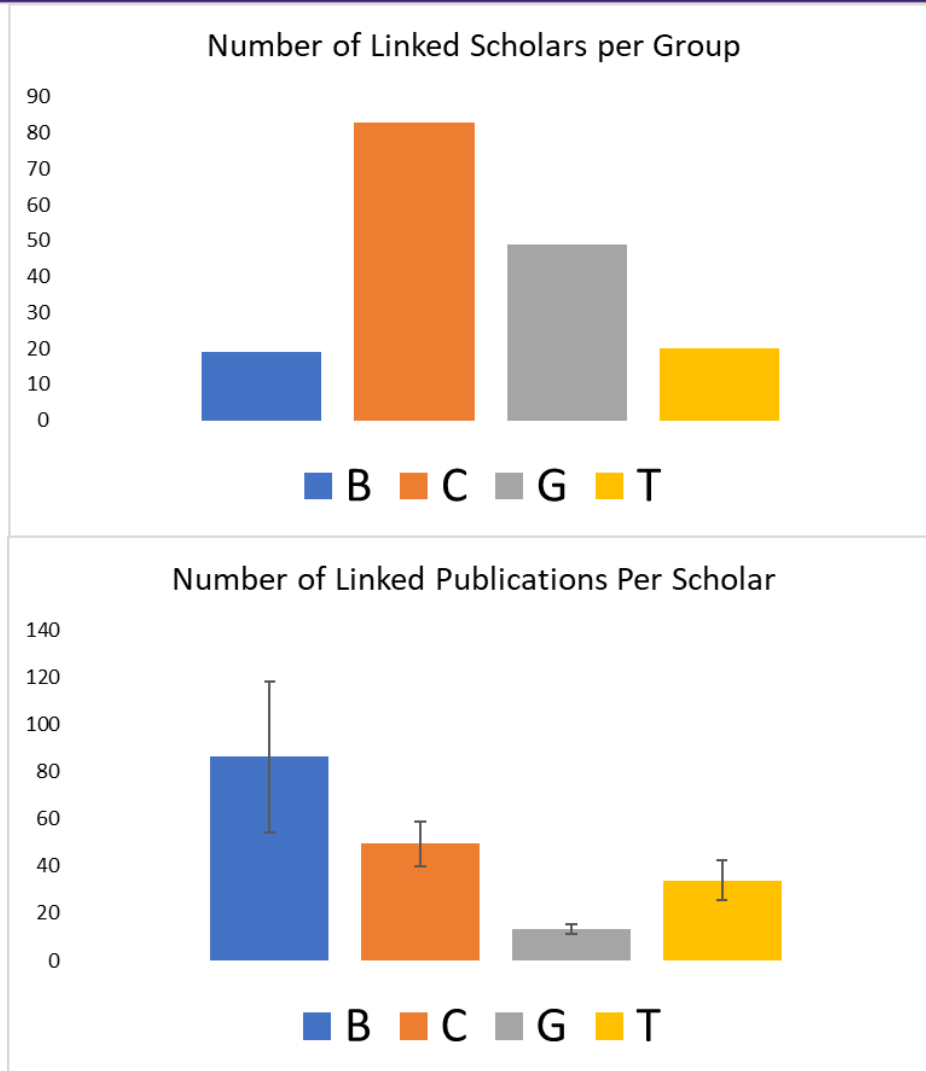
Most of the 207 V Scholars in the analysis were classified as C type, followed by G, T, and B.

But: The average number of linked publications was largest for the B-type grants, followed by C, T, and G. The differences were highly significant (p<0.01).

B = biomarker or genomic signature
C = cancer biology
G = general cell biology
T = treatment-related

VF Results: Time to Impact

The average time for G grant linkage was 11.2 years, whereas T grant publications were quoted significantly faster (average 7.8 years)

Average Time (Years) Between Scholar Publication and PACE CII Piece of Evidence
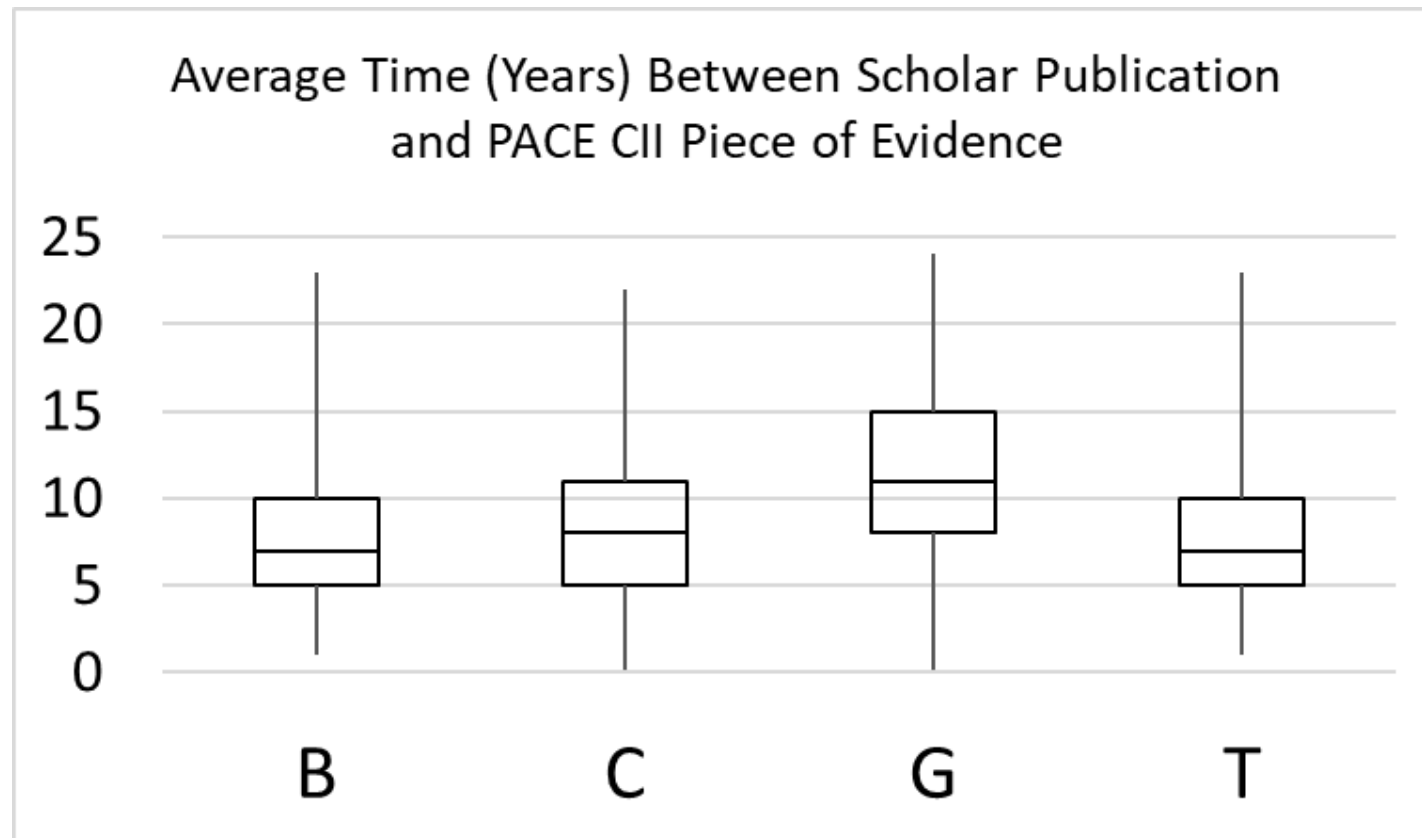
Boxplot: Median, first and third quartile, and total range are shown. p<0.0001

B = biomarker or genomic signature

C = cancer biology

G = general cell biology

T = treatment-related

VF Results: Summary

- Number of linked grants and time to impact differed by grant type
  - B and T grants created significantly more and faster impact
- G grants more likely to have longer chains of citations
  - *Investments in basic research require time and iteration before impacting clinical practice*
- G grants had highest percentage of scholars with no connections
  - *Funding basic research may be higher risk*
  - *Even after >11 years on average, we may still not have waiting long enough to see the ultimate impact*
- The distribution of grant types shifted over time
  - Shift from G grants toward more B and T grants over time

BCRF Investigators

- 159 prominent breast cancer researchers funded between 1992-2011
- Classified by BCRF into six major categories:

1 = biology

2 = etiology

3 = prevention
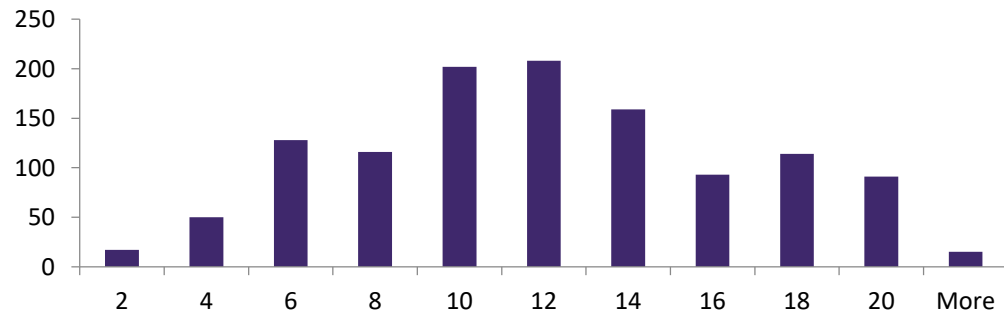
4 = early detection / prognosis
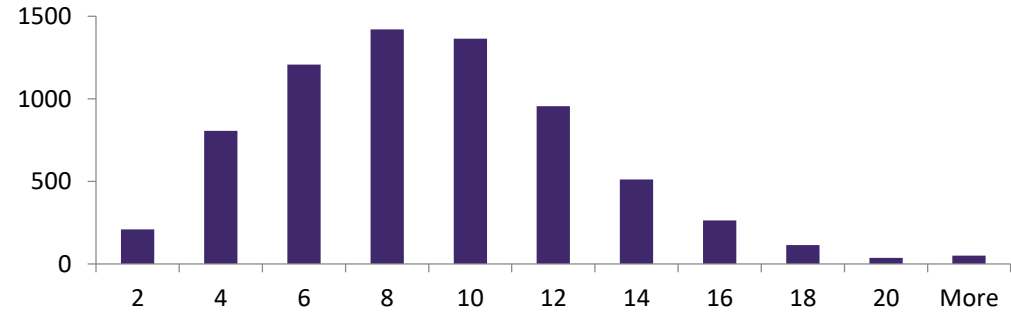
5 = treatment
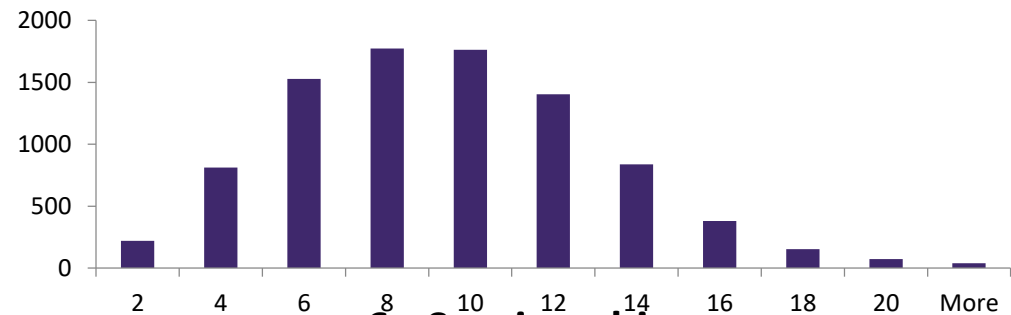
6 = survivorship

BCRF Results: Number of Linkages

- 142 of 159 investigators (~90%) had at least one linkage

- 28 investigators (~18%) had first degree linkages

Histogram - How many grantees had 50, 100, 150, etc. links?
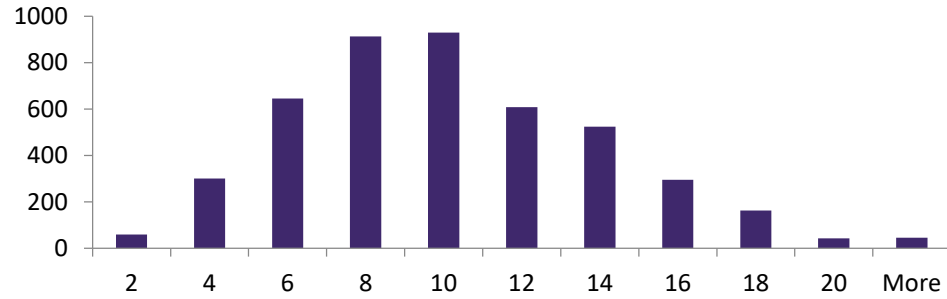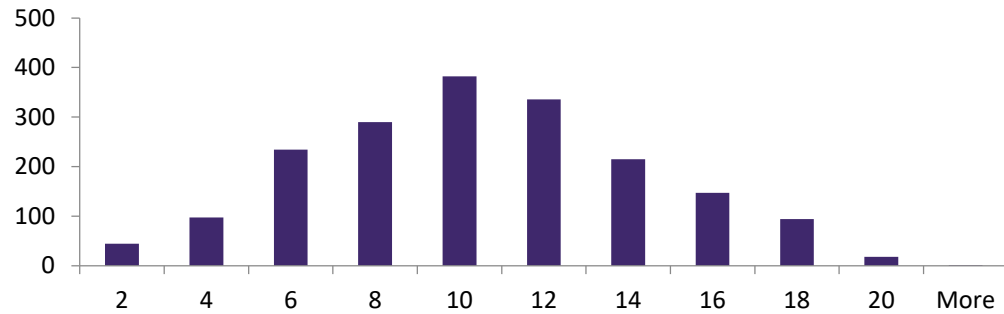
BCRF Results: Time to Impact
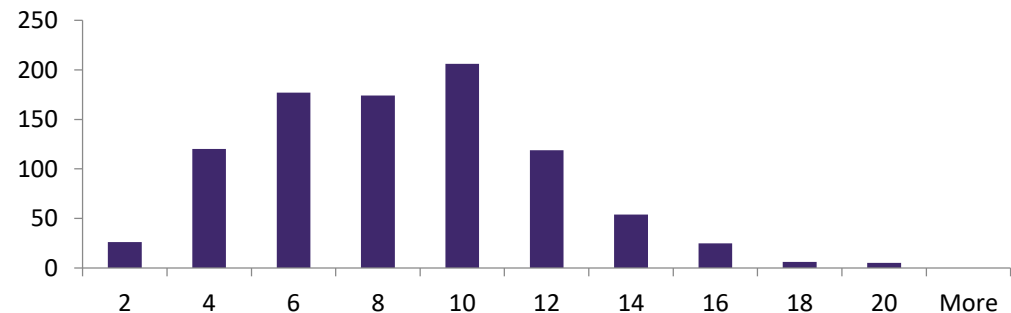
BCRF Results: Analysis of Variance

The first 3 categories constitute a group with slower impact compared to the last 3 categories.
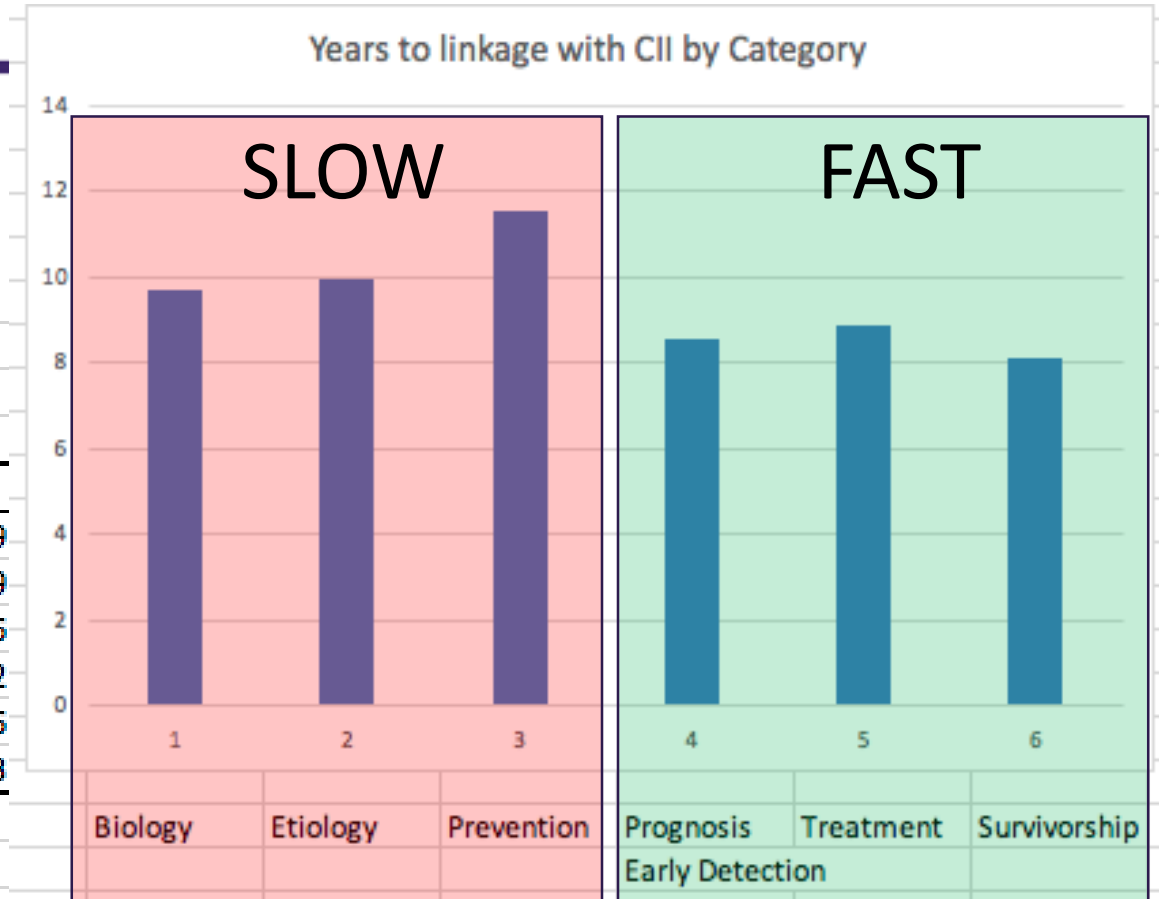
Anova: Single Factor

SUMMARY

Groups	Count	Sum	Average	Variance
Column 1	4524	43721	9.66423519	15.5270779
Column 2	1858	18531	9.97362756	15.3256369
Column 3	1193	13758	11.5322716	21.2239996
Column 4	6940	59268	8.54005764	14.877052
Column 5	8982	79895	8.89501225	14.1759266
Column 6	912	7383	8.09539474	11.5682773

ANOVA

Source of Variat.	SS	df	MS	F	P-value	F crit
Between Gr	13382.1201	5	2676.42401	178.903697	1.157E-187	2.21446569
Within Grou	365072.25	24403	14.9601381			
Total	378454.37	24408				

Years to linkage with CII by Category

	SLOW			FAST		
	1	2	3	4	5	6
	Biology	Etiology	Prevention	Prognosis	Treatment	Survivorship
				Early Detection		

BCRF Results: Summary

- We identified linkages for nearly 90% of investigators

- Time to impact differs significantly across grant types
  - Biology, etiology, and prevention grants take longer to impact the clinical literature than early detection / prognosis, treatment, and survivorship grants

- Composition of BCRF portfolio was stable over time (p = 0.92)

- Two grant categories strongly influenced by single grantees
  - Etiology (12 investigators had >50 linkages, 4 had >100)
  - Prevention (4 investigators had >100 linkages, 1 had >800)

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Overall Summary Results

- The **pattern of impact by grant type was similar** between the two datasets.
  - *Funders can use these consistent differences as one dimension to construct and manage a portfolio of grants with the desired mix of short/long-term risk/impact.*
- Compared to the VF study, the BCRF dataset generally had more links per scholar. This is likely due to all research being focused on breast cancer, one of the cancers in the CII. The VF scope is much broader and includes cancers not in the CII (e.g., leukemias, childhood cancers).
- The BCRF dataset has a lot more first-level linkages than the VF, because the BCRF funds investigators who focus on clinical trials or those whose work ranges from basic biology to clinical trials.
- Both analyses highlighted many **individual impact stories**.

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Example Story – Bench to Bedside

1994 Basic science identifies a new mechanism for treatment resistance

2006 Cell line work on the resistance mechanism shows how it can be reversed

2011 More work in cell lines demonstrates how a specific new treatment can reverse the resistance

2013 Phase II trial shows efficacy of this new treatment

2018 …ongoing: Phase III trial now running…

Green: Publication from BCRF investigator.

Blue: Evidence from the PACE CII database.

Orange: This story is continuing. Research takes time.

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Lessons Learned

- Time horizon for impact
  - 10+ years
  - Varies on portfolio mix
- Collecting data
- Characterizing portfolio
- Communicating success stories
  - Most successes are not quick breakthroughs
  - Finding clear, concise ways to communicate complex and cumulative achievements is a challenge – but it is possible!

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Challenges	Solutions
Name disambiguation	Maintain bibliographies from grantees Middle initials Curated commercial databases
Categorizing grants in portfolio	Consider portfolio goals Collect with other routine data if possible
Self-citation; insular citation networks Citing reviews instead of primary sources	Read papers to see citations in context; ensure they are meaningful and positive
Big papers with 400 co-authors	Consider excluding from analysis
Attribution of impact in case of multiple funders	Challenging. This method is better suited for differences between groups than absolute statements
Communicating complex success stories	Simplify, but provide context Acknowledge interactions with other contributions to realize greater long-term achievements

What do I need to do something like this?

- Some technical coding skills or partnerships

- Data on existing and past grants

- Set of publications representing key achievements
  - Cancer – PACE CII freely available at http://scoringprogress.com
  - Other disease areas
    - Identify set of seminal papers
    - Fields with no treatments – collect data, categorize, ID goals for each domain, ID pivotal papers in that domain, then work backwards

- Contact us!
  Samuel.Thomas@roseliassociates.com

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NCBI E-Utilities

- Programming interface to NIH databases, including PubMed
- Compatible with any computer language that can send a URL to the E-utilities server and interpret the XML response
  - Examples: Perl, Python, Java, and C++
- https://www.ncbi.nlm.nih.gov/books/NBK25497/
- https://www.youtube.com/watch?v=BCG-M5k-gvE

Entrez Programming Utilities Help

NCBI Help Manual

National Center for Biotechnology Information

U.S. National Library of Medicine

Identifying Seminal Papers

- Clinical guidelines citations

- Cochrane reviews

- "Advances in [disease of interest] Research"

INTERAGENCY AUTISM COORDINATING COMMITTEE

2017
SUMMARY
OF ADVANCES
in Autism Spectrum Disorder Research

IACC
INTERAGENCY AUTISM COORDINATING COMMITTEE

OFFICE OF AUTISM RESEARCH COORDINATION
NATIONAL INSTITUTES OF HEALTH

Peer-Reviewed, Published Consensus Papers   www.tsalliance.org

The following papers are available free of charge with open access to anyone in the world. The TS Alliance encourages sharing these links, or a link to this page (tsalliance.org/consensus) with healthcare providers. Any future updates to these recommendations will also be posted on this page.

- Northrup H et al. Tuberous Sclerosis Complex **Diagnostic Criteria Update**: Recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference, *Pediatric Neurology* (October 2013)
- Krueger DA et al. Tuberous Sclerosis Complex **Surveillance and Management**: Recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference, *Pediatric Neurology* (October 2013)
- Roth J et al. Subependymal Giant Cell Astrocytoma: Diagnosis, Screening, and Treatment. Recommendations From the International Tuberous Sclerosis Complex Consensus Conference 2012, *Pediatric Neurology* (December 2013)
- Leclezio L et al. Pilot Validation of the Tuberous Sclerosis-Associated Neuropsychiatric Disorders (TAND) Checklist, *Pediatric Neurology* (January 2015)
- deVries PJ et al. Tu[...]
- Hinton RB et al. Ca[...] and management [...] (November 2014).
- Teng JMC et al. De[...] Dermatology (Octo[...]

Tuberous Sclerosis Complex Surveillance and Management: Recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference

Darcy A. Krueger MD PhD [a,*], Hope Northrup MD [b], on behalf of the International Tuberous Sclerosis Complex Consensus Group

Cites 58 key studies

IACC publishes annual list of ~20 top advances in Autism Spectrum Disorder research

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