Culture changes in health research

Data sharing issues related to the STRATOS initiative, prognostic research and meta analysis

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Overview

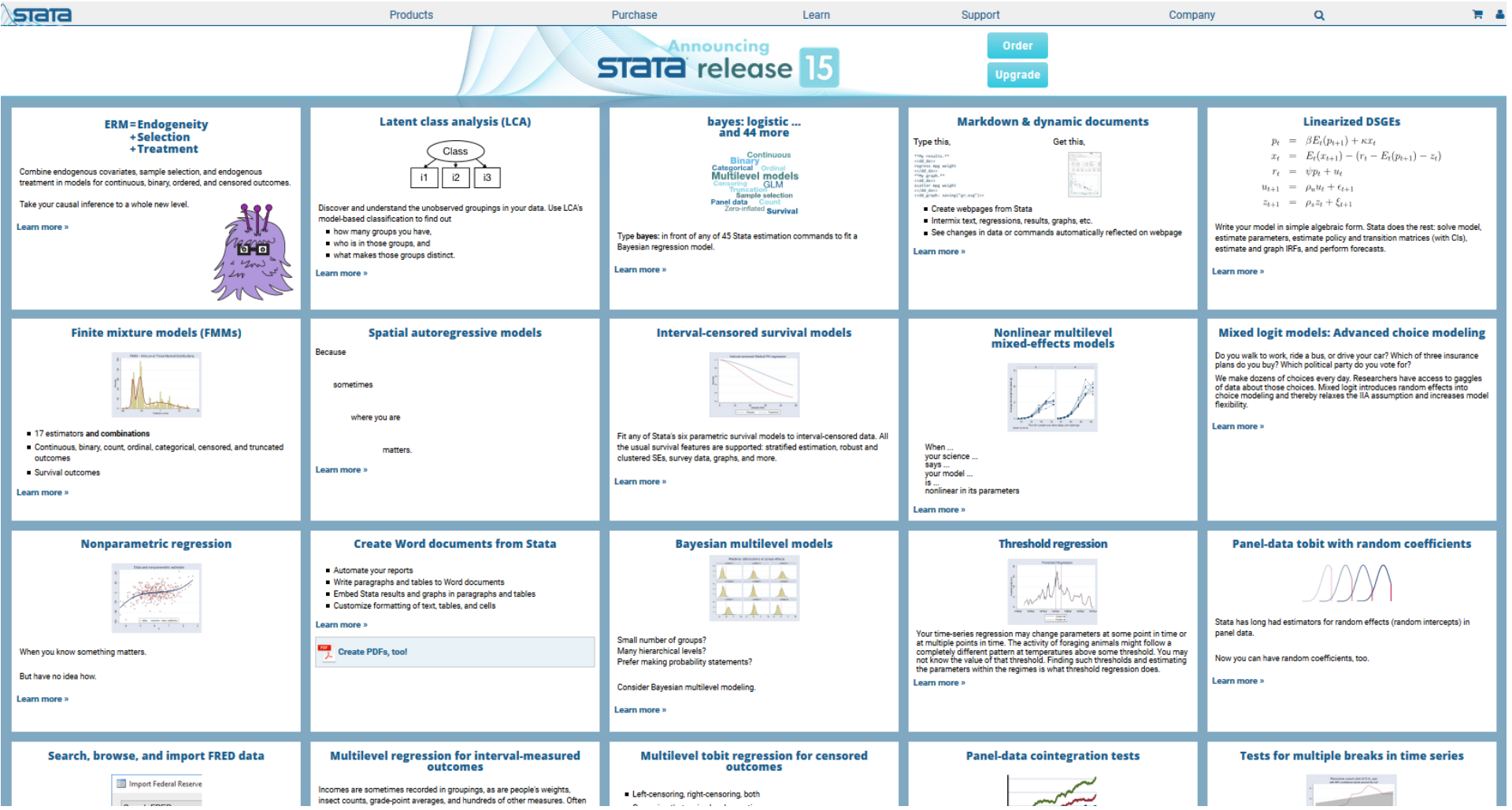
- Introduction of the **STRengthening Analytical Thinking for Observational Studies** initiative
- Relevance of guidance for statistical analyses of observational studies.
- Relevance of data sharing
  - STRATOS
  - Prognostic research
- IPD meta-analysis
- Final remarks

The STRATOS initiative – WHY?
Current situation in statistical methodology

- Statistical methodology has seen some substantial development
- Computer facilities can be viewed as the cornerstone
- Possible to assess properties and compare complex model building strategies using simulation studies
- Resampling and Bayesian methods allow investigations that were impossible two decades ago
- Wealth of new statistical software packages allows a rapid implementation and verification of new statistical ideas

Software package STATA

new procedures in 2018



Splines

a brief overview of regression packages in R

Package	Downloads	Vignette	Book	Website	Datasets
quantreg	2001231	X	X		7
mgcv	1438166	X	X		2
survival	1229305	X	X		33
VGAM	297308	X	X	X	50
gbm	271362			X	3
gam	168143		X	X	1
gamlss	78295	X	X	X	29

Perperoglou et al, talk at ISCB 2017, see STRATOS website

Current situation in practical analyses

- Unfortunately, many sensible improvements are ignored

Reasons why improved strategies are ignored

- Overwhelming concern with **theoretical aspects**
- Very **limited guidance** on key issues that are **vital in practice**, discourages analysts from utilizing more sophisticated and possibly more appropriate methods in their analyses

Statistical methodology – problems are well known

The severeness of problems is even discussed in the public press:

The Economist ‘Unreliable research: Trouble at the lab.’ (October 2013):

“Scientists’ grasp of statistics has not kept pace with the development of complex mathematical techniques for crunching data. Some scientists use inappropriate techniques because those are the ones they feel comfortable with; others latch on to new ones without understanding their subtleties. Some just rely on the methods built into their software, even if they don’t understand them.”

The Lancet Research:
Increasing Value, Reducing Waste Series

Comment (Introduction 1)

How should medical science change?

In 2009, we published a Viewpoint by Iain Chalmers and Paul Glasziou called "Avoidable waste in the production and reporting of research evidence", which made the extraordinary claim that as much as 85% of research investment was wasted.

Our belief is that research funders, scientific societies, school and university teachers, professional medical associations, and scientific publishers (and their editors) can use this Series as an opportunity to examine more forensically why they are doing what they do—the purpose of science and science communication—and whether they are getting the most value for the time and money invested in science.

Kleinert and Horton, 2014

The Lancet Research:
Increasing Value, Reducing Waste Series

Comment (Introduction 2)

- **Biomedical research: increasing value, reducing waste**

- Of 1575 reports about cancer prognostic markers published in 2005, 1509 (96%) detailed at least one significant prognostic variable. However, few identified biomarkers have been confirmed by subsequent research and few have entered routine clinical practice.
  ….
- Global biomedical and public health research involves billions of dollars and millions of people. In 2010, expenditure on life sciences (mostly biomedical) research was US$240 billion. The USA is the largest funder, with about $70 billion in commercial and $40 billion in governmental and non-profit funding annually, representing slightly more than 5% of US health-care expenditure. Although this vast enterprise has led to substantial health improvements, many more gains are possible if the waste and inefficiency in the ways that biomedical research is chosen, designed, done, analysed, regulated, managed, disseminated, and reported can be addressed.

Macleod et al., 2014

Better use of statistical methods

- At least two tasks are essential:
  1. **Experts** in specific methodological areas have to work towards **developing guidance**
  2. An ever-increasing need for **continuing education** at all stages of the career
- For busy applied researchers it is often difficult to follow methodological progress even in their principal application area
  - Reasons are diverse
  - Consequence is that analyses are often deficient
- **Knowledge** gained through research on statistical methodology needs to be **transferred** to the broader community
- Many **analysts** would be **grateful for** an overview on the current **state of the art** and for **practical guidance**

Aims of the initiative

- **Provide evidence supported guidance** for highly relevant issues in the design and analysis of observational studies
- As the **statistical knowledge** of the analyst **varies** substantially, guidance has to keep this background in mind. **Guidance** has to be provided **at several levels**
- For the **start** we will concentrate on **state-of-the-art** guidance and the necessary evidence
- Help to identify questions requiring much more primary research

The overarching long-term aim is to improve key parts of design and statistical analyses of observational studies in practice

Different levels of statistical knowledge

Level 1: Low statistical knowledge

• Most analyses are done by analysts at that level

Level 2: Experienced statistician

• Methodology perhaps slightly below state of the art, but doable by every experienced analyst

Level 3: Expert in a specific area

• To improve statistical models and to adapt them to complex real problems, researches develop new and more complicated approaches. Advantages and usefulness in practice need to be assessed

STRengthening Analytical Thinking for Observational Studies: the STRATOS initiative

Willi Sauerbrei,[a*†] Michal Abrahamowicz,[b] Douglas G. Altman,[c] Saskia le Cessie,[d] and[‡] James Carpenter[e] on behalf of the STRATOS initiative

Statistics in Medicine 2014

2011	ISCB Ottawa, Epidemiology Sub-Comm.	Preliminary ideas
2012	ISCB Bergen	Discussions, SG
2013	ISCB Munich	Initiative launched
2014-16	ISCB	Invited Sessions
2016	**BIRS**	**First general meeting**
2016	IBC Victoria	Invited Session
2016	HEC Munich	Invited Session
2017	IBS-EMR Thessaloniki	Invited Session
2017	ISCB Vigo	Scientific topic
2017	CEN-ISBS Vienna	Invited Session
2017	GMDS Oldenburg	Invited Session
2018	ISCB, RSS, …	Invited Sessions
2019	**BIRS**	**Second general meeting**

http://www.stratos-initiative.org/

Topic groups

Topic Group		Chairs and further members	
1	Missing data	Chairs:	James Carpenter, Kate Lee
		Members:	Melanie Bell, Els Goetghebeur, Joe Hogan, Rod Little, Andrea Rotnitzky, Kate Tilling, Ian White
2	Selection of variables and functional forms in multivariable analysis	Chairs:	Georg Heinze, Aris Perperoglou, Willi Sauerbrei
		Members:	Michal Abrahamowicz, Heiko Becher, Harald Binder, Daniela Dunkler, Frank Harrell, Patrick Royston, Matthias Schmid
3	Initial data analysis	Chairs:	Marianne Huebner, Saskia le Cessie, Werner Vach
		Members:	Maria Blettner, Dianne Cook, Heike Hofmann, Lara Lusa, Carsten Oliver Schmidt
4	Measurement error and misclassification	Chairs:	Laurence Freedman, Victor Kipnis
		Members:	Raymond Carroll, Veronika Deffner, Kevin Dodd, Paul Gustafson, Ruth Keogh, Helmut Küchenhoff, Pamela Shaw, Janet Tooze
5	Study design	Chairs:	Mitchell Gail, Suzanne Cadarette
		Members:	Doug Altman, Gary Collins, Stephen Evans, Neil Pearce, Peggy Sekula, Elizabeth Williamson, Mark Woodward
6	Evaluating diagnostic tests and prediction models	Chairs:	Gary Collins, Carl Moons, Ewout Steyerberg
		Members:	Patrick Bossuyt, Petra Macaskill, David McLernon, Ben van Calster, Andrew Vickers
7	Causal inference	Chairs:	Els Goetghebeur, Ingeborg Waernbaum
		Members:	Bianca De Stavola, Saskia le Cessie, Niels Keiding, Erica Moodie, Michael Wallace
8	Survival analysis	Chairs:	Michal Abrahamowicz, Per Kragh Andersen, Terry Therneau
		Members:	Richard Cook, Pierre Joly, Torben Martinussen, Maja Pohar-Perme, Jeremy Taylor, Hans van Houwelingen
9	High-dimensional data	Chairs:	Lisa McShane, Joerg Rahnenfuehrer
		Members:	Axel Benner, Harald Binder, Anne-Laure Boulesteix, Tomasz Burzykowski, Riccardo De Bin, W. Evan Johnson, Lara Lusa, Stefan Michiels, Eugenia Migliavacca, Sherri Rose, Willi Sauerbrei

Cross-cutting panels

Panel		Chairs and further members	
MP	**Membership**	Chairs:	James Carpenter, Willi Sauerbrei
PP	**Publications**	Chairs:	Bianca De Stavola, Stephen Walter
		Co-Chairs:	Mitchell Gail, Petra Macaskill
		Members:	Suzanne Cadarette, Simon Day, Marianne Huebner, Catherine Quantin, Joerg Rahnenfuehrer, Willi Sauerbrei, Pamela Shaw, Jeremy Taylor
GP	**Glossary**	Chairs:	Simon Day, Marianne Huebner, Jim Slattery
		Members:	Martin Boeker, Willi Sauerbrei, Carsten Oliver Schmidt, Peggy Sekula
WP	**Website**	Chairs:	Joerg Rahnenfuehrer, Willi Sauerbrei
		Members:	Ruth Keogh
RP	**Literature Review**	Chairs:	Gary Collins, Carl Moons
BP	**Bibliography**	Chairs:	to be determined
SP	**Simulation Studies**	Chairs:	Michal Abrahamowicz, Anne-Laure Boulesteix
		Members:	Harald Binder, Victor Kipnis, Jessica Myers Franklin, Willi Sauerbrei, Pamela Shaw, Ewout Steyerberg, Ingeborg Waernbaum
DP	**Data Sets**	Chairs:	Hermann Huss, Saskia Le Cessie, Aris Perperoglou
TP	**Knowledge Translation**	Chair:	Suzanne Cadarette
		Co-Chair:	Catherine Quantin
		Members:	Harbajan Chadha-Boreham
CP	**Contact Organizations**	Chairs:	Doug Altman, Willi Sauerbrei

Guidance for analysis is needed for many stakeholders (analysts with different levels of knowledge, teachers, reviewers, journalists, ……)

Researchers

First in a Series of Papers for the Biometric Bulletin

STRATOS initiative – Guidance for designing and analyzing observational studies

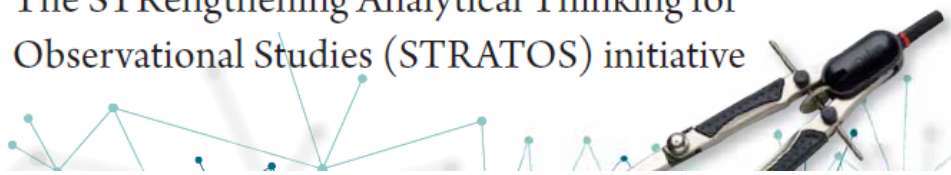
STRATOS INITIATIVE

Willi Sauerbrei[1], Marianne Huebner[2] , Gary S. Collins[3], Katherine Lee[4], Laurence Freedman[5], Mitchell Gail[6], Els Goetghebeur[7], Joerg Rahnenfuehrer[8] and Michal Abrahamowicz[9] on behalf of the STRATOS initiative.

Consumers

Guidance for designing and analysing observational studies:

The STRengthening Analytical Thinking for Observational Studies (STRATOS) initiative



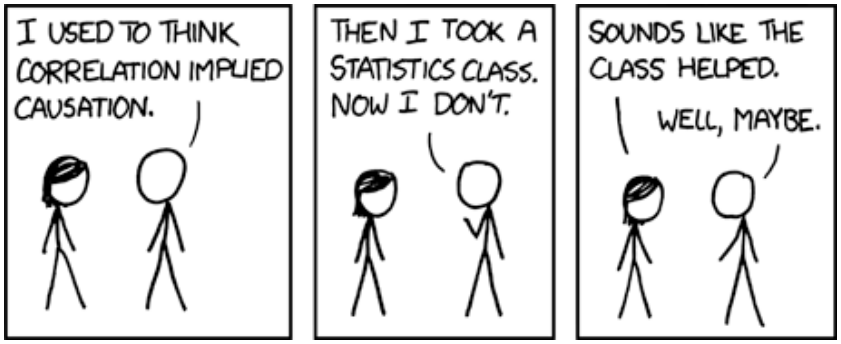
Willi Sauerbrei[1], Gary S. Collins[2], Marianne Huebner[3], Stephen D. Walter[4], Suzanne M. Cadarette[5], and Michal Abrahamowicz[6] on behalf of the STRATOS initiative

Volume 26 Number 3 | **Medical Writing** September 2017 | 17

Journal of the European Medical Writers Association (EMWA)

Relevance of guidance for statistical analyses of observational studies

- Identifying causal effects is the aim of many studies, but how?



Comic from xkcd.com

- In general, complex model building is required. Which confounders are required?
- What about the functional form of continuous variables?
- Is there a „state of the art“?

Selection of variables and functional forms in multivariable analysis (TG2 of STRATOS) - issues

- Which strategies for variable selection exist?
  What about their properties?
- Data-dependent modeling introduces bias.
  What about the role of shrinkage approaches?
- Comparison of spline procedures in a univariate context.
  Which criteria are relevant? Can we derive guidance for practice?
- What about variables with a 'spike-at-zero'?
- Multivariable procedures
  MFP well defined strategy
  Which of the spline based procedures?
  Comparison in large simulation studies needed
- Multivariable procedures and correction for selection bias
  How relevant? One step or two step approaches?
  E.g. selection of variables and forms followed by shrinkage
- Big Data
  Does it influence properties of procedures and their comparison?
- Role of model validation

The research community is far away from state of the art - much research is required!

General issues in many studies

- missing data (TG1)
- measurement error (TG4)
- was the study well designed ? (TG5)
- Initial data analysis (TG3)

  Improved pre-processing may also help to share data
- …..

miracum

Medical Informatics for Research and Care in University Medicine

#1

FEB 2018

Die Standardisierung der Analysen ist wichtig

Bei der Analyse der Patientendaten sind folgende Punkte von großer Wichtigkeit: (i) Reproduzierbarkeit, (ii) Dokumentation und (iii) Transparenz. Es zeigt sich in ver-

Melanie Börries, S. 44

» Sind die Daten interpretiert und so visualisiert, dass der behandelnde Onkologe sie nutzen kann, navigiert ihn die Systemmedizin durch eine Art Koordinaten-system. «

Melanie Börries

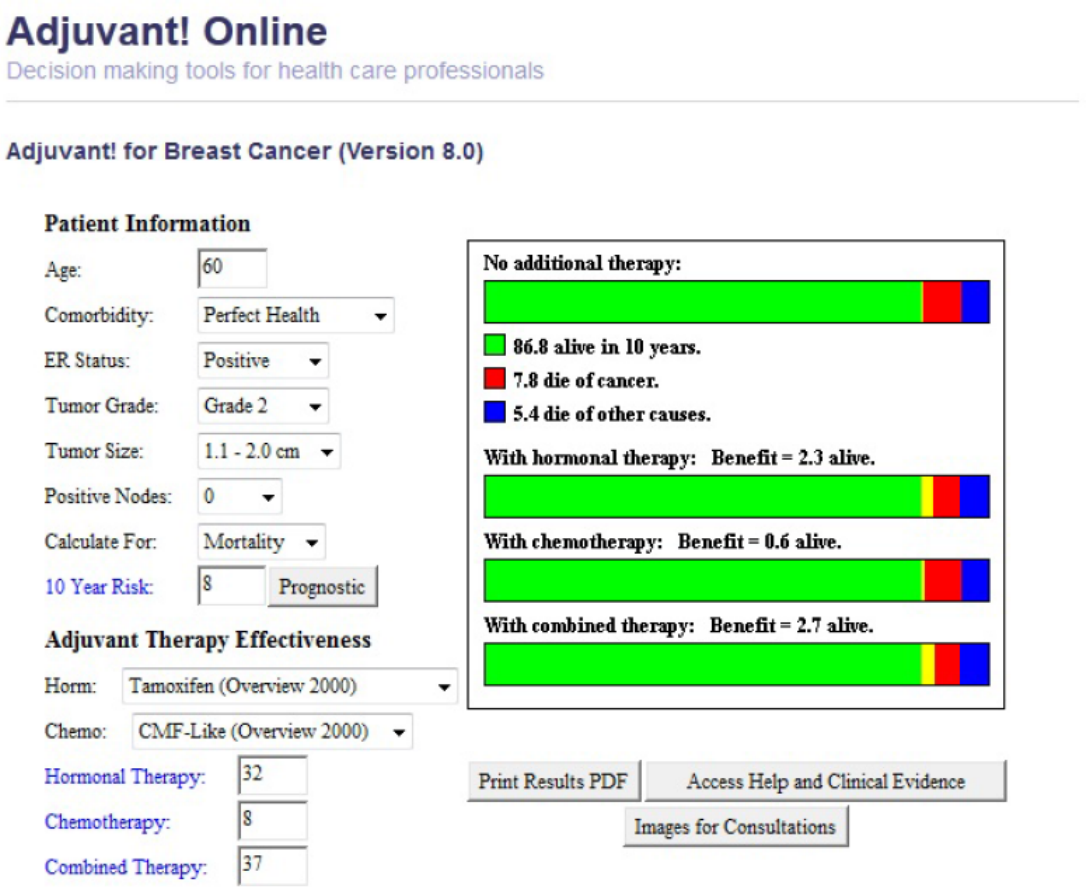
S. 43

Zustimmung!
Aber WIE schaffen wir das???

Wie kann man das Ergebnis einer Random Forest Analyse transparent darstellen?

Medical decision-making

Dream of doctors and patients



But it has been **OFFLINE** for several years

Data Sharing- first experiences

This report on the treatment of early breast cancer is being published in two successive weeks. Part 1 gives the general introduction and hormonal results; part 2 will give the cytotoxic therapy and immunotherapy results, and the general discussion of all results.

Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy

133 randomised trials involving 31 000 recurrences and 24 000 deaths among 75 000 women

EARLY BREAST CANCER TRIALISTS' COLLABORATIVE GROUP

The Lancet 1992 , Volume 339 , Issue 8784 , 1 - 15

Data Sharing – further experiences

J. R. Statist. Soc. A (1999)
162, *Part* 1, *pp.* 71–94

Building multivariable prognostic and diagnostic models: transformation of the predictors by using fractional polynomials

W. Sauerbrei

University of Freiburg, Germany

and P. Royston

Imperial College School of Medicine, London, UK

The data used in the paper can be obtained from

`http://www.blackwellpublishers.co.uk/rss/`

Data Sharing

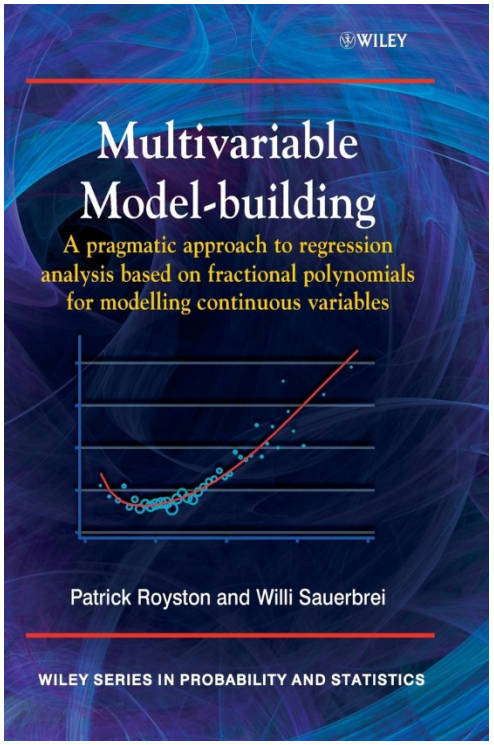


Table A.2 Datasets used more than once in our book. N/A = not applicable. Further details are given in Appendix A.2.

Name	Outcome	Obs.	Events	Variables[a]	Section reference
Research body fat	Cont.	326	N/A	1	1.1.3, 4.2.1, 4.9.1, 4.9.2, 4.10.3, 4.12
GBSG breast cancer	Survival	686	299	9	1.1.4, 3.6.2, 5.6.2, 6.5.2, 6.5.3, 6.5.4, 6.6.5, 6.6.6, 6.8.2, 7.6, 7.7.2, 8.8, 9.6
Educational body fat	Cont.	252	N/A	13	2.7.2, 2.8.6, 5.2, 5.3.1, 5.5.1, 8.5
Glioma	Survival	411	274	15	2.7.3, 8.4
Prostate cancer	Cont.	97	N/A	7	3.6.2, 3.6.3, 4.15, 6.2, 6.3.2, 6.4.2, 6.4.3, 6.5.1, 6.5.3, 6.6.1, 6.6.2, 6.6.3, 6.6.4, 7.11.3
Whitehall I	Survival	17 260	2576	10	6.7.3
	Binary	17 260	1670	10	4.13.1, 4.13.2, 4.14, 7.11.1, 7.11.3
PBC	Survival	418	161	17	5.3.2, 5.4, 5.5.2, 9.8
Oral cancer	Binary	397	194	1	6.7.1, 9.3.1
Kidney cancer	Survival	347	322	10	5.8.2, 7.9

- Data of 23 studies published (2008); http://mfp.imbi.uni-freiburg.de/
- Many (also unknown to us) colleagues agreed to make their data available
- Helpful **META-DATA** is important.

STRATOS – necessity of data sharing?

- STRATOS rules - as far as possible, papers should be open access, results should be reproducible, with data and software made available in conjunction with the publication.
- Each TG needs about 5-10 published ‚suitable' data sets for illustration. Some data sets should be usable from more than one TG.
- Specific problem of TG9 „High dimensional data": Omics data published, but often problems with data quality and documentation. Unfortuntely, related clinical data is often missing.
- Specific problem of TG8 „Survival analysis" – long-term follow-up data required, including information relevant for analyses of multiple events (competing risk, multi-state models, recurrent events).

STRATOS – necessity of data sharing?

Not really, but would be most helpful and allows

- Easier identification of ‚suitable' data sets
- That the published results can be compared with results based on STRATOS guidance (..and help identifying severe weaknesses and errors).
- Improving knowledge translation of STRATOS guidance

Prognostic research

- Based on **observational** studies.
- Usually **retrospective** studies, which **increases problems** related to design, sample size, data quality, statistical knowledge of analyst, reporting, publication bias, …
- Even before the omics time started, hundreds of prognostic markers and many prognostic models were proposed
- Only a small number of markers and models is **validated** and used in practice.
- **Omics** data offer promising opportunities but with severe **challenges and problems**.
- Obviously, **evidence-based** investigations concerning the value of markers and models are needed. Consequently, **systematic reviews and meta-analyses** are needed.

Meta-analysis of observational studies

- Currently no STRATOS TG, but we may start one in the future.
- Investigation of the effect of continuous factors is not possible without individual patient data (IPD)!!!
- MAs to investigate risk factors, prognostic factors, …… have severe problems if IPD is not available.

BAG-1 as a biomarker in early breast cancer prognosis: a systematic review with meta-analyses

E S Papadakis[1], T Reeves[*,1], N H Robson[1], T Maishman[3], G Packham[1] and R I Cutress[1,2]

[1]*Cancer Research UK Centre Cancer Sciences Unit, University of Southampton Faculty of Medicine, Southampton General Hospital, Tremona Road, Southampton SO16 6YD, UK;* [2]*University Hospital Southampton, University of Southampton Faculty of Medicine, Southampton General Hospital, Tremona Road, Southampton SO16 6YD, UK and* [3]*Southampton Clinical Trials Unit, University of Southampton, Southampton SO17 1BJ, UK*

Br J Cancer. 2017

- First view - SR, assessment of reporting quality (according to REMARK) and MA
- Key steps required for an evidence-based biomarker assessment

Assessment of studies according to REMARK reporting guidelines

Table 1. Studies of BAG-1 expression in breast cancer

	Tang *et al*, 1999	Turner *et al*, 2001	Townsend *et al*, 2002	Cutress *et al*, 2003	O'Driscoll *et al*, 2003	Tang *et al*, 2004	Sirvent *et al*, 2004	Yun *et al*, 2005	Lin *et al*, 2008	Nadler *et al*, 2008	Yang *et al*, 2008	Millar *et al*, 2009	Athanasiadou *et al*, 2009	Afentakis *et al*, 2013	Wang *et al*, 2014	Dowsett *et al*, 2015	Papadakis *et al*, 2016	Davidson *et al*, 2016
Introduction																		
Marker	BAG-1, PR, ER	BAG-1, BCL2, P53, ER, PR	BAG-1,HSC70	BAG-1	BAG-1, survivin, survivin-DEx3, survivin-2B, galectin-3, Bcl-2,MRP-1, Bax-a	BAG-1 Bcl-2 P53	BAG-1 Bcl-2 P53 BAX	BAG-1	BAG-1	BAG-1 Bcl-2	BAG-1	BAG-1	BAG-1 CD24	BAG-1	Bag-1 Parp-1 EGFR	GRB7, HER2, Cyclin B1, Ki-67, MYLB2, STK15, Survivin, BCL2, CUBE2, ER, PgR, Cathepsin L2, Stromelysin, BAG-1, CD68, GSTM1, ACTB, GAPDH, GUS, RPLPO, TFRC	BAG-1	BAG-1, HSP70, HSP90
Objectives	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Hypotheses	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Materials and methods																		
Patients																		
Disease stage	I-IV	I-II	IV	I-IV	I-III	I-IV	I-II	I-III	I-IV	I-IV	I-III	I-IV	I-IV	I-III	I-III	I-III	I-III	I-III
Disease subtype	Not limited by specific subtype	Not limited by specific subtype	Not limited by specific subtype	Not limited by specific subtype	Not limited by specific subtype	Not limited by specific subtype	Ductal	Not limited by specific subtype	Not limited by specific subtype	Not limited by specific subtype	Not limited by specific subtype	Ductal	Not limited by specific subtype	ER positive	Not limited by specific subtype	ER positive	Not limited by specific subtype	Not limited by specific subtype
Co-morbidities	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×
Inclusion/ exclusion criteria	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Treatment received	Not limited by specific treatment	Not limited by specific treatment	Not limited by specific treatment	Not limited by specific treatment	Not limited by specific treatment	Not limited by specific treatment	Not limited by specific treatment	Not limited by specific treatment	Not limited by specific treatment	Not limited by specific treatment	Not limited by specific treatment	Not limited by specific treatment	Not limited by specific treatment	Tamoxifen or anastrazole	Not limited by specific treatment	Tamoxifen or anastrazole	Not limited by specific treatment	Not limited by specific treatment
Treatment randomised	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×
Specimen																		
Type	PTS	PTS	PTS	PTS	PTS	PTS	PTS	PTS	PTS	PTS	PTS	PTS	PTS	PTS	PTS	PTS	PTS	PTS
Controls	PTN	N	PTN	PTN	N	PTN	PTN	N	PTN	PTN	PTN	N	PTN	PTN	PTN	PTN	N	PTN
Assay																		
Tissue sample	whole sections + IHC	whole sections + IHC	whole sections + IHC	whole sections + IHC	whole sections + RT-PCR	whole sections + IHC	whole sections + IHC	whole sections + IHC	Microarray	Microarray	Microarray	Microarray	Imprint smear + IHC	Microarray	Microarray	whole sections + RT-PCR	whole sections + RT-PCR	Microarray

Papadakis et al (2017)

- Identified 18 papers, providing results from 20 studies
- Assessed quality of reporting by REMARK criteria
- Performed ‚meta-analysis'

However, we identified severe weaknesses

(Sauerbrei & Haeussler (2018), British Journal of Cancer)

„This study illustrates key steps required for an evidence-based biomarker assessment; however, we have identified several major weaknesses in the assessment of the quality of reporting and the meta-analyses. We concluded **that results and inferences from this study are not justified by the assessments and analyses presented**."

Reply of Papadakis et al:
„We felt that this was **important**, particularly since BAG-1 is already included in multi-gene assays widely used as **part of routine clinical practice**..."

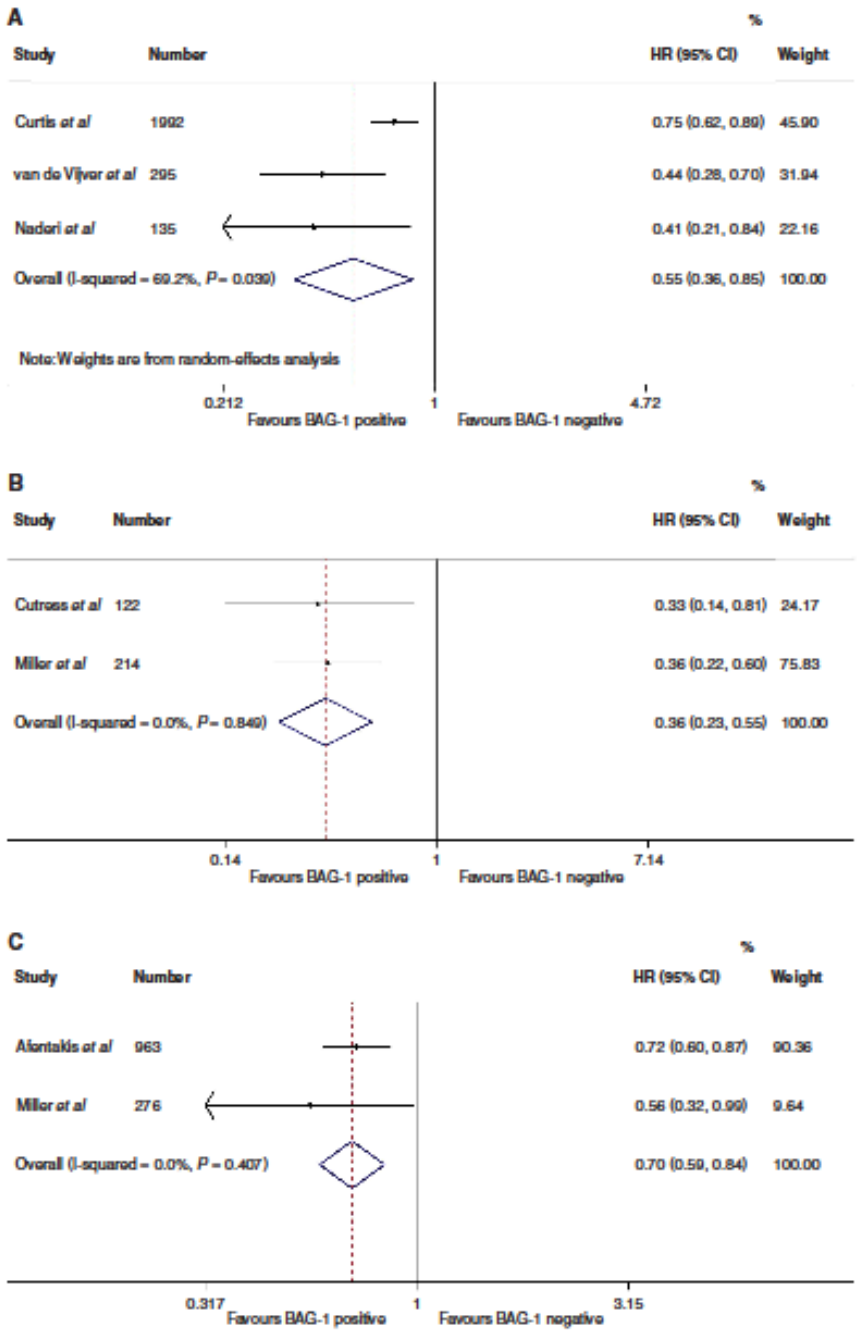
Comment on Papadakis et al (2017)

1. Assessment of the quality of reporting according to REMARK
   - Overly **positive assessment** of reporting, strongly **contradicting** a recent review on the topic (Sekula et al. 2017)
     - ‚rationale for sample size' – positively assessed in all studies by Papadakis et al, vs. 22%, 11% and 8% in Sekula et al.
   - Several shortcomings in **reporting of the primary** literature found - examples:
     - Rationale for sample size:
       - *‚All patients with histopathological confirmation of breast cancer, diagnosed […] between 1995 and 2001, were included [only 70 patients included].'*
     - Multivariable analysis:
       - No effect estimates, only p-values in several studies or indication of non-significance

Comment on Papadakis et al (2017)

2. Meta-analysis

'In general, data were too heterogeneous, and outcome measures were too varied to perform meta-analyses for the majority of studies. Meta-analyses of mRNA expression from the two data sets analysed in Millar et al (2009) and the data set analysed in Papadakis et al (2016) including a total of 2422 patients produced a HR of 0.55 (95% CI 0.36–0.85) favouring improved BCSS with high expression of BAG-1'



Three ‚meta-analyses' published

Several issues

- 14 out of 18 papers ignored
- Combination of multivariable and univariate analyses
- Variable definitions of BAG-1 positivity

Comment on Papadakis et al (2017)

3. Meaningful meta-analyses of biomarkers – individual participant data (IPD) required
   - Primary study – multivariable model required (effect adjusted for potential confounders)
   - Meta-analysis – combine ‚adjusted effects‘

Collaboration between study groups and IPD required

4. Publication bias and the need for a comprehensive biomarker study registry

Meta-analyses based on published data

Primary studies:

- Use different cutpoints for continuous variables
- Adjust for different confounders
- Reporting is insufficient. Estimates from multivariable models are needed but are often not provided
- Different measurement techniques are used – which studies can be combined?

IPD meta-analyses – are they feasible?

IPD projects are difficult but many good projects have been started.

Abo-Zaid et al found 48 published IPD meta-analyses of prognostic factors (published 1991 – March 2009, several inclusion criteria).

However, it is obvious that reporting and analysis of IPD projects need improvement.

Individual participant data meta-analysis of prognostic factor studies: *state of the art?*

Abo-Zaid *et al. BMC Medical Research Methodology* 2012, **12**:56

Cooperative IPD projects are possible (1)

- In traumatic brain injury, researchers initiated IMPACT (International Mission for Prognosis and Analysis of Clinical Trials) and meta-analysed IPD from 11 studies including 9,205 patients [Marmarou et al, 2007].
- http://www.tbi-impact.org/?p=publications
- 62 publications listed.

Probably more, most recent listed is from 2013.

Cooperative IPD projects are possible (2)

- The **Emerging Risk Factors Collaboration (ERFC)** is a CEU-led consortium of >130 prospective studies from >30 countries
- IPD collated and harmonized from ~2.5M participants
- Cardiovascular diseases risk factors and cause-specific mortality studied in greater detail by IPD meta-analysis.
- Risk factors studied included: circulating lipid markers, inflammatory markers, glycaemia markers, adiposity markers, diabetes, and cardio-metabolic multi-morbidity.
- Analyses concern etiological hypothesis or risk prediction assessment in subsets of studies/participants with relevant data, **with methodological developments** occurring in parallel as necessary.

http://www.phpc.cam.ac.uk/ceu/erfc/

ERFC

Emerging Risk Factors Collaboration

OPEN ACCESS Freely available online

PLOS | MEDICINE

Guidelines and Guidance

Improving the Transparency of Prognosis Research: The Role of Reporting, Data Sharing, Registration, and Protocols

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Peat et al. (2014) PLoS Med 11(7): e1001671

Improving the Transparency of Prognosis Research: The Role of Reporting, Data Sharing, Registration, and Protocols

Summary Points

- Prognosis research is concerned with predicting outcomes to make health care more effective. It has a crucial role to play in clinical and policy decision-making.
- The quality of much prognosis research is poor, evidenced by incomplete reporting, poor data sharing, incomplete registrations, and absent study protocols.
- Initiatives to improve transparency in trials include reporting guidelines, data pooling, registers, and journal requirements for protocols. Prognosis research could be transformed by similar initiatives.
- Routine registration of all prognostic studies, linked to an accessible study protocol using agreed reporting guidelines, would improve transparency and promote data sharing.
- Concern about applying transparency methods to observational research could be resolved by flexibility to update date-stamped protocols during prognosis studies.

Peat et al. (2014) PLoS Med 11(7): e1001671

Potential benefits of study registration, protocol publication, better study reporting, and data sharing of prognosis research studies

Potential Benefit	Registration	Protocols	Reporting	Sharing
Ethical				
Respect the investigator-participant covenant to generate new, publicly accessible biomedical knowledge of potential value to future patients	X	X	X	X
Facilitate monitoring and accountability in relation to global standards for ethical research, including informed consent	X	X	X	
Cost-effective use of public money	X	X	X	X
Scientific				
Improve the quality and reliability of evidence from prognosis research, (and thereby enhance impact on health and health care)	X	X	X	X
Help accelerate knowledge creation through easier identification of and access to full study details, including data, in order to increase opportunities for collaboration including systematic reviews and meta-analysis	X	X	X	X
Answer research questions only possible through collaboration				X
Reduce unnecessary duplication of invested research resources through awareness of existing studies	X	X		
Establish intellectual property		X		
Provide a denominator against which publication bias can be assessed	X	X		
Provide means for identification and prevention of biased under-reporting or over-reporting of research		X	X	
Involve patients in studies, including enrolment	X	X		
Peer review of protocols to improve study quality and refine methods		X		
Methodological issues sufficiently detailed to, in principle, allow study replication (details not always allowable in published reports)		X		

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Peat et al. (2014) PLoS Med 11(7): e1001671

PROGRESS recommendations

1. Full study reporting through use of guidelines
2. Facilitate and expect data sharing
3. Routine registration of all prognosis studies using existing registers
4. Protocols for all prognosis studies made public
5. Promote systematic development and evaluation of methods and value of transparency

Peat et al. (2014) PLoS Med 11(7): e1001671

Meta analysis of observational studies

- Examples concentrate on prognostic research but methodological problems are very similar in other fields
- Publication bias is a key problem
- Which studies to include in a MA??
- ‚Well defined population of studies‘
  - decreases number of studies
  - may allow to estimate combined effects unbiasedly (Sekula et al 2017)

Evidence based assessment and application of prognostic markers – it is a long way from single studies to meta-analysis (Sauerbrei et al 2006)

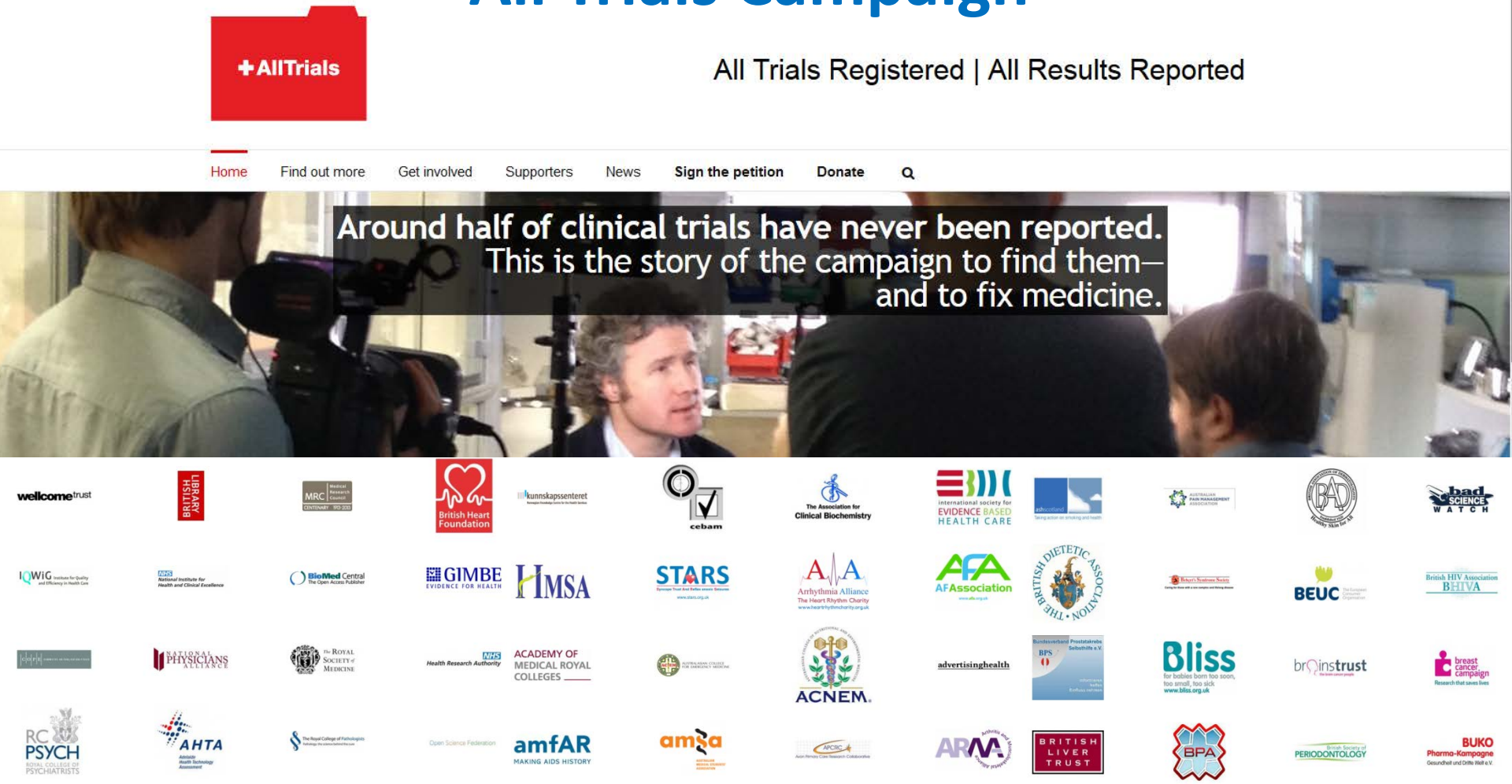
Further projects, initiatives and rules strongly arguing for

reproducible research

and

data sharing

All Trials Campaign



91043 people and 737 organizations have signed the AllTrials petition.

www.alltrials.net

Guidelines for Code and Data Submission

Specific Guidance on Reproducible Research (RR)

Benjamin Hofner, Fabian Scheipl (RR Editors, Biometrical Journal)
E-mail: fabian.scheipl@stat.uni-muenchen.de

Document Version: 1.7 (2016/10/28)

4 Example

A good example is given by W. Sauerbrei, A. Buchholz, A.-L. Boulesteix & H. Binder (see http://onlinelibrary.wiley.com/enhanced/doi/10.1002/bimj.201300222/).

On stability issues in deriving multivariable regression models

Willi Sauerbrei[*,1], **Anika Buchholz**[1], **Anne-Laure Boulesteix**[2], and **Harald Binder**[3]

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Biometrical Journal (2014)

Problems of data sharing in Germany

- Interest to collaborate?
- Consent of patients
- Data protection rules
- Different measurement techniques
- Follow-up data

Incentive to share data

- Involvement in relevant and interesting projects
- Publications
- Citations related to published data
- Help improving research – may be useful for me as a patient

Final remarks

- At least for evidence based assessments closer collaboration among disciples and among study groups is required.
- Data sharing is required.
- Funders of prognosis research should require data sharing with appropriate governance (Peat et al 2014).
- To improve analyses, methodologists need to work and agree on guidance for many relevant relevant issues.
- Partly it may help to borrow ideas and suitable instruments from clinical research.
- The lowest hanging fruit: GOOD REPORTING! http://www.equator-network.org/

Problems of current research are known!

The tumor marker research community must come to the same realization that clinical trialists came to decades ago. **If** sound scientific principles of careful study design, adequate study size, scrupulous data collection and documentation, and appropriate analysis strategies are **not adhered to**, the field **will flounder**. Culture changes will be required.

Identification of Clinically Useful Cancer Prognostic Factors: What Are We Missing?

Lisa M. McShane, Douglas G. Altman, Willi Sauerbrei

Editorial in JNCI 2005

We should not forget

Weaknesses in analyses can have severe consequences for patients

"A mistake in the operating room can threaten the life of one patient; a mistake in statistical analysis or interpretation can lead to hundreds of early deaths. So it is perhaps odd that, while we allow a doctor to conduct surgery only after years of training, we give SPSS to almost anyone."

Andrew Vickers [*Nat Clin Pract Urol* 2005]

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