Culture changes in health research
Data sharing issues related to the STRATOS initiative, prognostic research and meta analysis

Willi Sauerbrei
Institute of Medical Biometry and Statistics
Medical Center – University of Freiburg, Germany
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**

<table>
<thead>
<tr>
<th>Package</th>
<th>Downloads</th>
<th>Vignette</th>
<th>Book</th>
<th>Website</th>
<th>Datasets</th>
</tr>
</thead>
<tbody>
<tr>
<td>quantreg</td>
<td>2001231</td>
<td>X</td>
<td>X</td>
<td></td>
<td>7</td>
</tr>
<tr>
<td>mgcv</td>
<td>1438166</td>
<td>X</td>
<td>X</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>survival</td>
<td>1229305</td>
<td>X</td>
<td>X</td>
<td></td>
<td>33</td>
</tr>
<tr>
<td>VGAM</td>
<td>297308</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>50</td>
</tr>
<tr>
<td>gbm</td>
<td>271362</td>
<td></td>
<td></td>
<td>X</td>
<td>3</td>
</tr>
<tr>
<td>gam</td>
<td>168143</td>
<td></td>
<td>X</td>
<td>X</td>
<td>1</td>
</tr>
<tr>
<td>gamlss</td>
<td>78295</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>29</td>
</tr>
</tbody>
</table>

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.”
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.
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, Michal Abrahamowicz, Douglas G. Altman, Saskia le Cessie, and James Carpenter
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/
<table>
<thead>
<tr>
<th>Topic Group</th>
<th>Chairs and further members</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Missing data</td>
<td>Chairs: James Carpenter, Kate Lee&lt;br&gt;Members: Melanie Bell, Els Goetghebeur, Joe Hogan, Rod Little, Andrea Rotnitzky, Kate Tilling, Ian White</td>
</tr>
<tr>
<td>2 Selection of variables and functional forms in multivariable analysis</td>
<td>Chairs: Georg Heinze, Aris Perperoglou, Willi Sauerbrei&lt;br&gt;Members: Michal Abrahamowicz, Heiko Becher, Harald Binder, Daniela Dunkler, Frank Harrell, Patrick Royston, Matthias Schmid</td>
</tr>
<tr>
<td>3 Initial data analysis</td>
<td>Chairs: Marianne Huebner, Saskia le Cessie, Werner Vach&lt;br&gt;Members: Maria Blettner, Dianne Cook, Heike Hofmann, Lara Lusa, Carsten Oliver Schmidt</td>
</tr>
<tr>
<td>4 Measurement error and misclassification</td>
<td>Chairs: Laurence Freedman, Victor Kipnis&lt;br&gt;Members: Raymond Carroll, Veronika Deffner, Kevin Dodd, Paul Gustafson, Ruth Keogh, Helmut Küchenhoff, Pamela Shaw, Janet Tooze</td>
</tr>
<tr>
<td>5 Study design</td>
<td>Chairs: Mitchell Gail, Suzanne Cadarette&lt;br&gt;Members: Doug Altman, Gary Collins, Stephen Evans, Neil Pearce, Peggy Sekula, Elizabeth Williamson, Mark Woodward</td>
</tr>
<tr>
<td>6 Evaluating diagnostic tests and prediction models</td>
<td>Chairs: Gary Collins, Carl Moons, Ewout Steyerberg&lt;br&gt;Members: Patrick Bossuyt, Petra Macaskill, David McLernon, Ben van Calster, Andrew Vickers</td>
</tr>
<tr>
<td>7 Causal inference</td>
<td>Chairs: Els Goetghebeur, Ingeborg Waerbaum&lt;br&gt;Members: Bianca De Stavola, Saskia le Cessie, Niels Keiding, Erica Moodie, Michael Wallace</td>
</tr>
<tr>
<td>8 Survival analysis</td>
<td>Chairs: Michal Abrahamowicz, Per Kragh Andersen, Terry Therneau&lt;br&gt;Members: Richard Cook, Pierre Joly, Torben Martinussen, Maja Pohar-Perme, Jeremy Taylor, Hans van Houwelingen</td>
</tr>
</tbody>
</table>
## Cross-cutting panels

<table>
<thead>
<tr>
<th>Panel</th>
<th>Chairs and further members</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MP</strong></td>
<td><strong>Membership</strong></td>
</tr>
<tr>
<td>Chairs:</td>
<td>James Carpenter, Willi Sauerbrei</td>
</tr>
<tr>
<td><strong>PP</strong></td>
<td><strong>Publications</strong></td>
</tr>
<tr>
<td>Chairs:</td>
<td>Bianca De Stavola, Stephen Walter</td>
</tr>
<tr>
<td>Co-Chairs:</td>
<td>Mitchell Gail, Petra Macaskill</td>
</tr>
<tr>
<td>Members:</td>
<td>Suzanne Cadarette, Simon Day, Marianne Huebner, Catherine Quantin, Joerg Rahnenfuehrer, Willi Sauerbrei, Pamela Shaw, Jeremy Taylor</td>
</tr>
<tr>
<td><strong>GP</strong></td>
<td><strong>Glossary</strong></td>
</tr>
<tr>
<td>Chairs:</td>
<td>Simon Day, Marianne Huebner, Jim Slattery</td>
</tr>
<tr>
<td>Members:</td>
<td>Martin Boeker, Willi Sauerbrei, Carsten Oliver Schmidt, Peggy Sekula</td>
</tr>
<tr>
<td><strong>WP</strong></td>
<td><strong>Website</strong></td>
</tr>
<tr>
<td>Chairs:</td>
<td>Joerg Rahnenfuehrer, Willi Sauerbrei</td>
</tr>
<tr>
<td>Members:</td>
<td>Ruth Keogh</td>
</tr>
<tr>
<td><strong>RP</strong></td>
<td><strong>Literature Review</strong></td>
</tr>
<tr>
<td>Chairs:</td>
<td>Gary Collins, Carl Moons</td>
</tr>
<tr>
<td><strong>BP</strong></td>
<td><strong>Bibliography</strong></td>
</tr>
<tr>
<td>Chairs:</td>
<td>to be determined</td>
</tr>
<tr>
<td><strong>SP</strong></td>
<td><strong>Simulation Studies</strong></td>
</tr>
<tr>
<td>Chairs:</td>
<td>Michal Abrahamowicz, Anne-Laure Boulesteix</td>
</tr>
<tr>
<td>Members:</td>
<td>Harald Binder, Victor Kipnis, Jessica Myers Franklin, Willi Sauerbrei, Pamela Shaw, Ewout Steyerberg, Ingeborg Waernbaum</td>
</tr>
<tr>
<td><strong>DP</strong></td>
<td><strong>Data Sets</strong></td>
</tr>
<tr>
<td>Chairs:</td>
<td>Hermann Huss, Saskia Le Cessie, Aris Perperoglou</td>
</tr>
<tr>
<td><strong>TP</strong></td>
<td><strong>Knowledge Translation</strong></td>
</tr>
<tr>
<td>Chair:</td>
<td>Suzanne Cadarette</td>
</tr>
<tr>
<td>Co-Chair:</td>
<td>Catherine Quantin</td>
</tr>
<tr>
<td>Members:</td>
<td>Harbajan Chadha-Boreham</td>
</tr>
<tr>
<td><strong>CP</strong></td>
<td><strong>Contact Organizations</strong></td>
</tr>
<tr>
<td>Chairs:</td>
<td>Doug Altman, Willi Sauerbrei</td>
</tr>
</tbody>
</table>
Guidance for analysis is needed for many stakeholders (analysts with different levels of knowledge, teachers, reviewers, journalists, ……)

Researchers

Consumers

First in a Series of Papers for the Biometric Bulletin

STRATOS initiative – Guidance for designing and analyzing observational studies

STRATOS INITIATIVE

Willi Sauerbrei¹, Marianne Huebner², Gary S. Collins³, Katherine Lee⁴, Laurence Freedman⁵, Mitchell Gail⁶, Els Goetghebeur⁷, Joerg Rahnenfuehrer⁸ and Michal Abrahamowicz⁹ on behalf of the STRATOS initiative.

Guidance for designing and analysing observational studies:
The STRengthening Analytical Thinking for Observational Studies (STRATOS) initiative

Volume 26 Number 3 | Medical Writing September 2017 | 17
Relevance of guidance for statistical analyses of observational studies

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

• 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
- .....
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

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
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

Data Sharing – further experiences

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

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

<table>
<thead>
<tr>
<th>Name</th>
<th>Outcome</th>
<th>Obs.</th>
<th>Events</th>
<th>Variables*</th>
<th>Section reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Research body fat</td>
<td>Cont.</td>
<td>326</td>
<td>N/A</td>
<td>1</td>
<td>1.1.3, 4.2.1, 4.9.1, 4.9.2, 4.10.3, 4.12</td>
</tr>
<tr>
<td>GBSG breast cancer</td>
<td>Survival</td>
<td>686</td>
<td>299</td>
<td>9</td>
<td>1.1.4, 3.6.2, 5.6.2, 5.6.3, 5.6.4, 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</td>
</tr>
<tr>
<td>Educational body fat</td>
<td>Cont.</td>
<td>252</td>
<td>N/A</td>
<td>13</td>
<td>2.7.2, 2.8.6, 5.2, 5.3.1, 5.5.1, 8.5</td>
</tr>
<tr>
<td>Glioma</td>
<td>Survival</td>
<td>411</td>
<td>274</td>
<td>15</td>
<td>2.7.3, 8.4</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>Cont.</td>
<td>97</td>
<td>N/A</td>
<td>7</td>
<td>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</td>
</tr>
<tr>
<td>Whitehall I</td>
<td>Survival</td>
<td>17260</td>
<td>2576</td>
<td>10</td>
<td>4.13.1, 4.13.2, 4.14, 7.11.1, 7.11.3</td>
</tr>
<tr>
<td>PBC</td>
<td>Survival</td>
<td>418</td>
<td>161</td>
<td>17</td>
<td>5.3.2, 5.4, 5.5.2, 9.8</td>
</tr>
<tr>
<td>Oral cancer</td>
<td>Binary</td>
<td>397</td>
<td>194</td>
<td>1</td>
<td>6.7.1, 9.3.1</td>
</tr>
<tr>
<td>Kidney cancer</td>
<td>Survival</td>
<td>347</td>
<td>322</td>
<td>10</td>
<td>5.8.2, 7.9</td>
</tr>
</tbody>
</table>
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. Unfortunately, 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 Papadakis¹, T Reeves*,¹, N H Robson¹, T Maishman³, G Packham¹ and R I Cutress¹,²

¹Cancer Research UK Centre Cancer Sciences Unit, University of Southampton Faculty of Medicine, Southampton General Hospital, Tremona Road, Southampton SO16 6YD, UK; ²University Hospital Southampton, University of Southampton Faculty of Medicine, Southampton General Hospital, Tremona Road, Southampton SO16 6YD, UK and ³Southampton 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

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Introduction</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Objectives</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hypotheses</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Materials and methods</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Patients</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Disease stage</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Disease subtype</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Comorbidities</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Inclusion/ exclusion criteria</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Treatment received</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Treatment randomised</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Specimen</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Type</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Controls</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Assay</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Tissue sample</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- CR177, H1GR, Cyclin D1, KL-6, MYC, STK15, Survivin, TSG2, CEP12, CR, Pgp1, Catenin, L2
- Estrogen, BAG-1, GD3, US14, ACR, GAPSH, GUS, HSP, TP, TPRC, BAG-1, HSP90, HSP90
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.


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

George Peat¹ 1, Richard D. Riley² 1, Peter Croft³, Katherine I. Morley⁴ 5, Panayiotis A. Kyzas⁶, Karel G. M. Moons⁷, Pablo Perel⁸, Ewout W. Steyerberg⁹, Sara Schroter¹⁰, Douglas G. Altman¹¹, Harry Hemingway¹², for the PROGRESS Group†

1 Arthritis Research UK Primary Care Research Centre, Research Institute for Primary Care & Health Sciences, Keele University, Keele, Staffordshire, United Kingdom, 2 School of Health and Population Sciences, University of Birmingham, United Kingdom, 3 Arthritis Research UK Primary Care Research Centre, Research Institute for Primary Care & Health Sciences, Keele University, Keele, Staffordshire, United Kingdom, 4 Department of Epidemiology and Public Health, University College London, London, United Kingdom, 5 Centre for Molecular, Environmental, Genetic and Analytic Epidemiology, The University of Melbourne, Victoria, Australia, 6 Department of Oral and Maxillofacial Surgery, North Manchester General Hospital, Pennine Acute NHS Trust, Manchester, United Kingdom, 7 Julius Center for Health Sciences and Primary Care, UMC Utrecht, Utrecht, Netherlands, 8 London School of Hygiene & Tropical Medicine, London, United Kingdom, 9 Department of Public Health, Erasmus MC, Rotterdam, Netherlands, 10 BMJ, London, United Kingdom, 11 Centre for Statistics in Medicine, University of Oxford, Wolfson College Annex, Oxford, United Kingdom, 12 Department of Epidemiology and Public Health and Director of the Farr Institute of Health Informatics Research at UCL Partners, London, United Kingdom

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.

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

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

doi:10.1371/journal.pmed.1001671.t002

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

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 Buchholz1, Anne-Laure Boulesteix2, and Harald Binder3

1 Department für Medizinische Biometrie und Medizinische Informatik, Universitätsklinikum Freiburg, Stefan-Meier-Str. 26, 79104 Freiburg, Germany
2 Institut für Medizinische Informationsverarbeitung, Biometrie und Epidemiologie, Ludwig-Maximilians-Universität München, Marchioninistr. 15, 81377 München, Germany
3 Institut für Medizinische Biometrie, Epidemiologie und Informatik, Universitätsmedizin der Johannes-Gutenberg-Universität Mainz, Obere Zahlbacher Straße 69, 55131 Mainz, Germany
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.”

Some selected references