Prognostic studies and the need for guidance

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STRATOS TG5: Study Design

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STRATOS TG5: Study Design

What does it involve?

- **Everything** around **planning/designing** a study
  … *study protocol*

Why is it important?

- Good design as basis for a convincing observational study
- By thorough planning severe errors can be avoided
  especially those that might not be repaired later on

Do we need (further) guidance?

YES

- New design options
- Empirical evidence ➡ prognostic studies

Biomarker studies

- Increasing number of biomarker studies in literature
- **Background:**
  - Advances in molecular biology and laboratory techniques allowing (large-scale) evaluation of different features in humans
  - Perception of high relevance for (future) clinical practice in which medical decisions are tailored to individuals
- **Areas of application:**

  screening / differential diagnostics / treatment choice / monitoring / **prognostics** / …

Prognostic biomarker

- Predicting progress of disease

- **Phases in development:** ***‚from bench to bedside‘***

(a) discovery → *TG9*

➡ (b) assay development

➡ (c) (retrospective) validation

➡ (d) prospective assessment → *TG6*

➡ (e) clinical implementation

Prognostic biomarker

Issue: only very few biomarkers reach clinical implementation

Malats *et al* (2005) [PMID: 16129368]

- **Background:** p53 (IHC) and bladder cancer
- **Aim:** comprehensive review for use of p53
- **Methods:** systematic review / meta-analysis
- **Conclusions:** evidence not sufficient for any conclusion

> "That a decade of research on P53 and bladder cancer has not placed us in a better position to draw conclusions relevant to the clinical management of patients is **frustrating**."

Prognostic biomarker

Huber *et al* (2014) [PMID: 25422912]

- **Background:** many prognostic biomarkers (IHC) for prostate cancer proposed w/o implemention
- **Aim:** verification of 28 IHC biomarkers
- **Design:** prostate cancer cohort ($N_{patients}$=238, N_{events}=?)
  median follow up 60 months
  outcome: PSA relapse-free survival
- **Results/Conclusion:**

  significant associations seen for 4/28 biomarkers (14%)

  ➡ Many IHC-based studies too over-optimistic

Issues of prognostic biomarker research

- ***‚Hot topic'*** – but not restricted to prognostic biomarker research

  McShane *et al* (2005): „What are we missing?"
  [PMID: 16030294]

  Kyzas *et al* (2007): „Almost all articles on cancer prognostic markers report statistically significant results"
  [PMID: 17981458]

- **Issues:**
  - Lack in agreed research goal, limited research funding
  - Poor study design
  - Incorrect methods, **NOT** restricted to statistical analysis
  - Faulty interpretation/presentation of results
  - Selective or incomplete reporting (incl. non-publication)

Way out for prognostic biomarker research

Examples:

- McShane *et al* (2005): reporting guideline REMARK
  [PMID: 16106245]
- Riley *et al* (2009): discussion of methodological issues
  [PMID: 19367280]
- Hemingway *et al* (2010): ten steps for improvement
  [PMID: 20042483]
- Andre *et al* (2011): call for biomarker study registry
  [PMID: 21364690]
- **...**

Way out for prognostic biomarker research

- **PROGRESS PARTNERSHIP**
  MRC PROGnosis RESearch Strategy Partnership

http://progress-partnership.org/

Is that not enough?

Observations from tumor marker prognostic studies

Sekula *et al* (2017) [PMID: 28614415]

Evaluation of 106 published studies (2007-2012)

- **Main aim:** to assess whether reporting quality improved

  ➡ **Conclusion:** still poorly reported

- Limited possibility to assess of methodological issues
- Prerequisite: transparent reporting

Observations from tumor marker prognostic studies

- **Study design:**

	N (%)
Prospective assessment	17 (16%)
Retrospective assessment based on …	
- prospectively conducted studies (incl. RCT)	33 (31%)
- archived specimen/data (incl. case registry)	56 (53%)

➡ Reflects special situation in cancer research

- Tumor patients are often closely monitored
- Routine collection of specimen, clinical data, outcome data
- Readiness of specimen/data for any retrospective evaluation

Observations from tumor marker prognostic studies

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Issue: selection bias

- Necessary assumption of representativeness and completeness of collection
- Even if correct, what about depletion of samples?

Observations from tumor marker prognostic studies

Issue: selection bias – completeness of patient data

- In presence of missing values, complete case analysis (?)
- Several reports, presentation of data suggests completeness

Example:

„Tumor samples were collected between November 1999 and August 2005,…"

- Retrospective assessment based on archived specimen
- No hint of incomplete data

Table 1 Clinicopathological characteristics of all patients *extract only*

Factors	COX-2		
	Negative $n = 368$	Positive $n = 493$	P
Age at diagnosis (years)			
≤35	35 (9.5)	23 (4.7)	0.005
>35	333 (90.5)	470 (95.3)	
Tumor stage			
T1	143 (38.9)	252 (51.1)	0.002
T2	216 (58.7)	233 (47.3)	
T3–4	9 (2.4)	8 (1.6)	
Node stage			
N0			603
N1			
N2			
N3	24 (6.5)	36 (7.3)	
Histologic grade			
I	41 (11.1)	122 (24.7)	<0.001
II	176 (47.8)	288 (58.4)	
III	151 (41.0)	83 (16.8)	
Estrogen receptor			
Mean ± SD (%)	37.9 ± 39.8	66.8 ± 31.0	<0.001[a]
Negative	171 (46.5)	59 (12.0)	<0.001
Positive	197 (53.5)	434 (88.0)	

Is incompleteness an exclusion criterion?

Observations from tumor marker prognostic studies

Issue: study power – sample size calculation

- Often critizised to be too small
- Studies rarely reported on any power calculation (<5%)
- # Analysed subjects: range 24 - ~4000 (<100: 19%)
- Presumably, study size depended on …
  - Availability of specimens and/or completeness of data
  - Resources (man power and/or funding)
  - Stage of biomarker development / research question
  - …

In summary

Regarding prognostic tumor marker studies:

- Research quality is heavily critizised by many researchers (methodologists) since several years
- First publications providing some guidance available
- Still, not (much) improvement visible

Regarding medical research in general:

- Many (all?) of presented issues exist in other areas as well
- Additional efforts are required

➡ STRATOS INITIATIVE

By providing additional guidance documents