The role of clinical trials in establishing and refining standards

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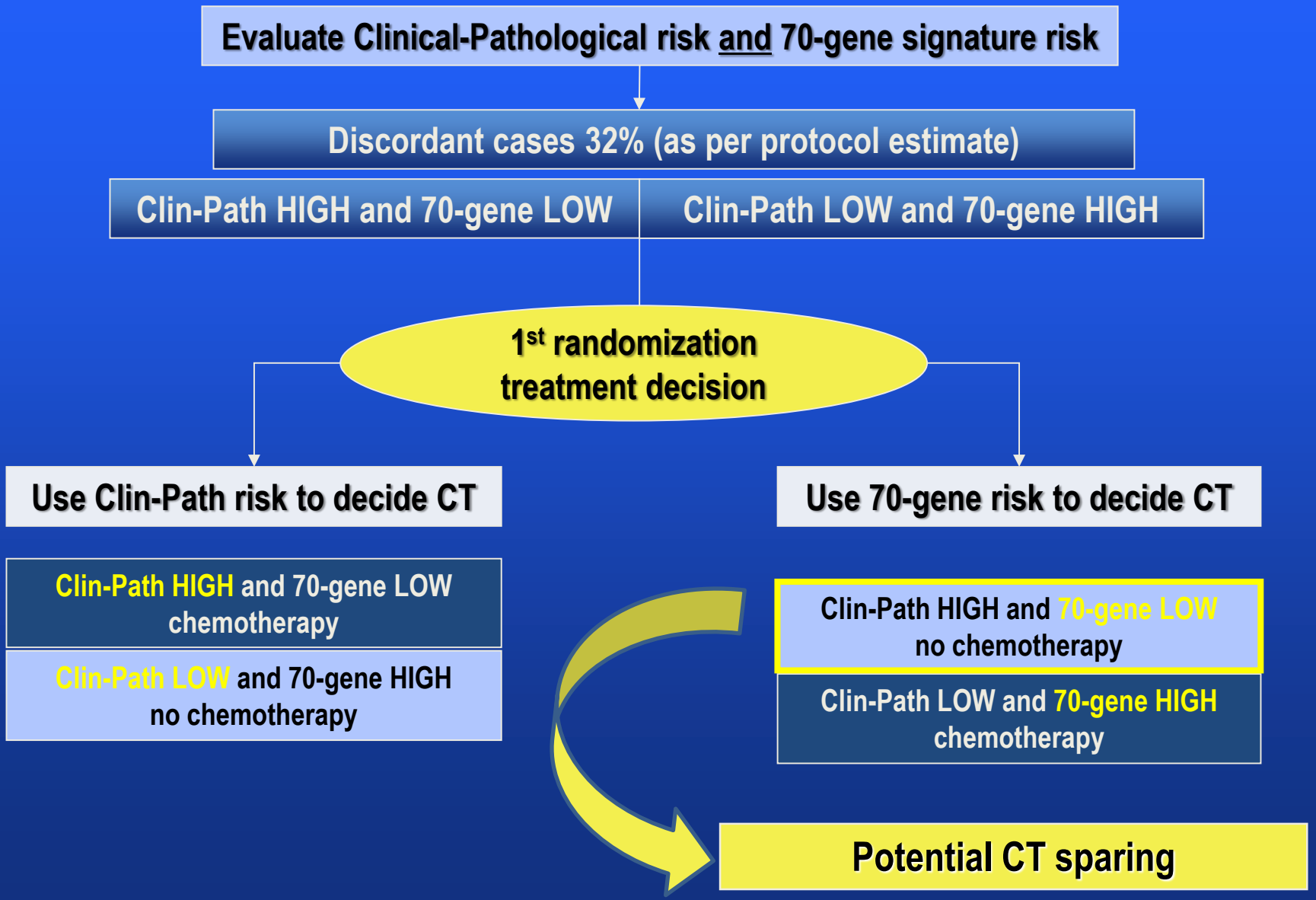
Let's take a 'simple' question

- EBC: chemo or no chemo?
- We go back 10 years:
  - StGallen criteria
  - Nottingham prognostic index
  - Adjuvant Online -> at that time reported to be used by >70% of clinicians as an information tool
- Organizing a clinical trial (high level evidence) on such a question is very hard …: CT vs no CT
- In these 10 years, 2 examples have been run, both in context of evaluating a genomic 'competing' tool: TAILORx in US for Oncotype DX (Genomic Health) and MINDACT in EU for Mammaprint (Agendia)

Why was AO the de facto standard?

- Some possible explanations:
  - Based on ‘most data’
  - Based on statistical approach, as compared to expert opinion
  - Available online, with a very easy calculator
  - Nice interactive tool
  - Free

EORTC-BIG MINDACT TRIAL DESIGN
The discordant cases



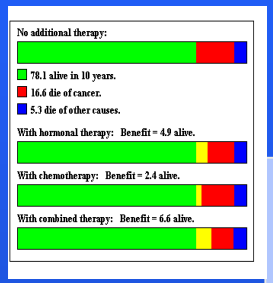
The single hardest question in all of this design?

- What is the standard way of deciding CT? In other words, the control arm was the problem
- First idea was: let investigator decide -> too much variability
- Finally:
- Adjuvant Online 10 year Breast cancer specific estimate defines good prognosis as:
  - > 88% without trt for ER+
  - > 92% without trt for ER-

MINDACT TRIAL DESIGN

EORTC European Organisation for Research and Treatment of Cancer

TRANSBIG

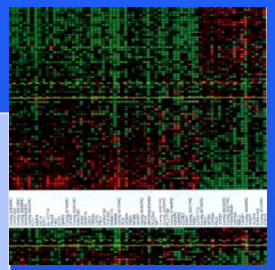


Registration & Screening
Surgery

N= 6600

Clinical-Pathological (C) risk
(Adjuvant! Online)

Genomic (G) risk
(70-gene MammaPrint signature)
And 44k complexe array from all



C-HIGH / G-HIGH

Discordant cases
C-HIGH / G-LOW or C-LOW / G-HIGH

C-LOW / G-LOW

1st randomization to treatment
use Clinical vs. Genomic risk

Chemotherapy

2nd randomization
Anthracycline –based vs. Capecitabine-Docetaxel

No Chemotherapy

HR+

Endocrine therapy

HR+

3rd randomization
Tamoxifen 2y / Letrozole 5y vs. Letrozole 7y

We recently returned to the ‘standard’ question

- Did a survey to revisit current practice, using MINDACT trial cases / profiles
- Will reassess when the data of MINDACT become available

Mindact Survey on adjuvant CT administration

Agreement in risk assessment among breast cancer specialists: a survey within the MINDACT cohort

C.A. Drukker, L. Slaets, R. Goossens, M.K. Schmidt, E.J.T. Rutgers, F. Cardoso, S.C. Linn, J. Bogaerts. Impakt 2015

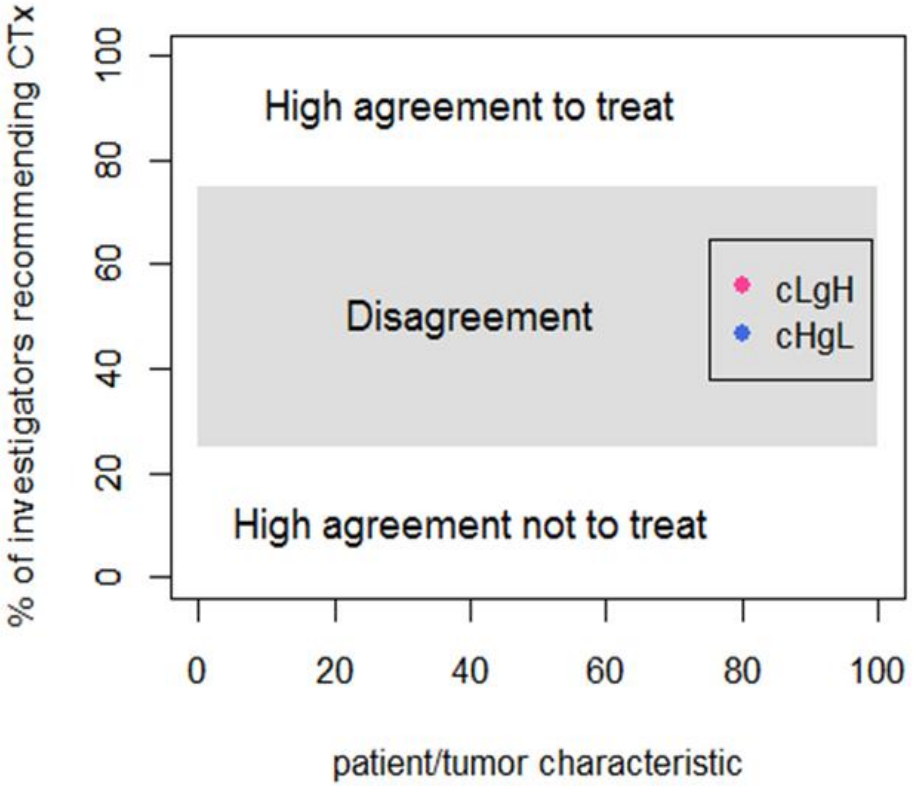
- 82 breast cancer specialists assessed 37 cases from the MINDACT trial and gave a recommendation for adjuvant chemotherapy (aCT).

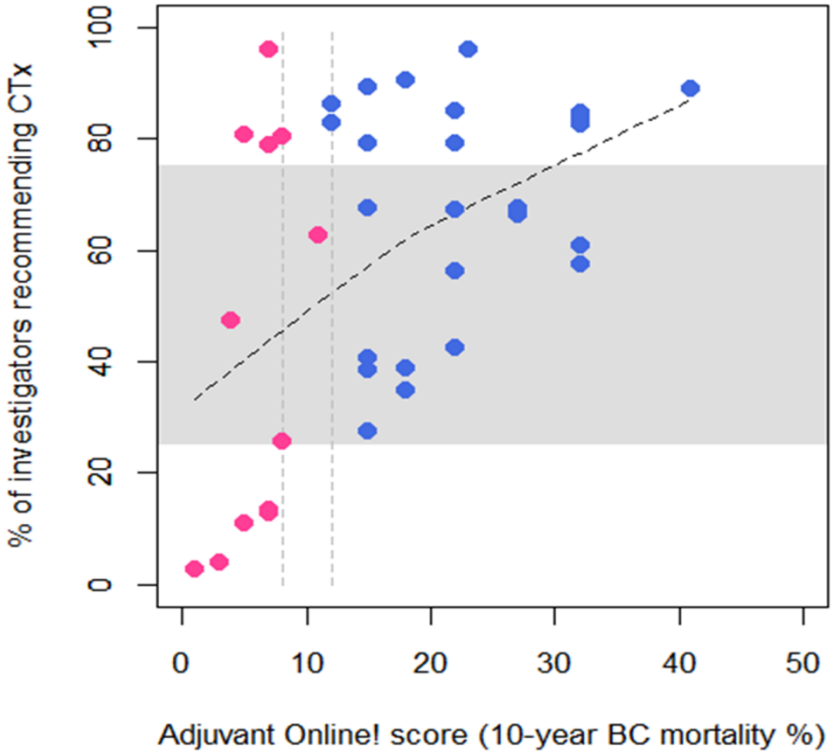
- The 37 cases have a discordant genomic (70 gene) vs. clinical ("Adjuvant Online!" - based cut-off (AOL)) risk assessment
  cases are either: AOL high – 70-gene signature low (cHgL) or
  AOL low – 70-gene signature high (cLgH)

- Cases were presented in an online questionnaire in a random order.
- Most participants were:
  medical oncologist (78%)
  at least 10 years of experience (76%).

Mindact Survey on adjuvant CT administration

The overall agreement between the participants and the Adjuvant Online! based decision rule was low (64%), with a lot of variation across cases (range 5% to 100%).





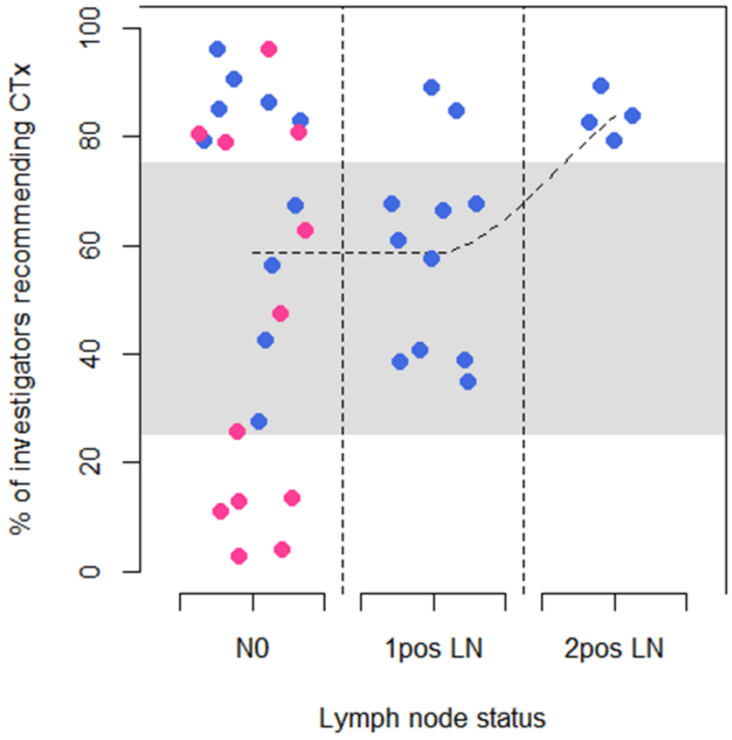
cLgH = clinical (m-AOL) low risk / genomic (MammaPrint) high risk case

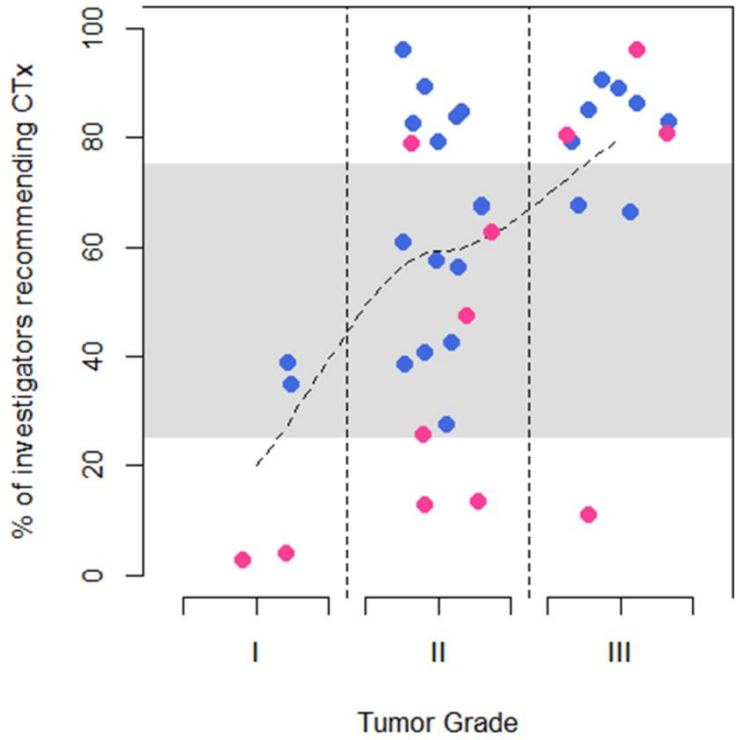
cHgL = clinical (m-AOL) high risk / genomic (MammaPrint) low risk case

Mindact Survey on adjuvant CT administration

There is in general a high agreement to administer aCT for patients:

- with high grade tumors
- and/or have at least 2 positive lymph nodes
- and/or who are of young age (<45).





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Mindact Survey on adjuvant CT administration

- The overall agreement among breast cancer specialists regarding the administration of aCT was low to moderate (77%) and varied greatly from case to case (range 53% to 96%).
- Apart from the cases involving
  - young patients,
  - high grade tumors
  - ≥2 positive lymph nodes,

  … **no clear patterns in aCT recommendation in relationship to other tumor characteristics were observed**. (!)

Some thoughts

- Treatment choices are an outcome of characteristics of
  - the patient (preferences)
  - the tumor/patient (prognostic and predictive)
  - the country's health system
  - the hospital/medical team
- How to implement, maintain, evaluate a standard?
- In case of CT decision, in my opinion a lot also depends on patient preference: toxicity vs efficacy
- Fact: we have insufficient information about true long term toxicity/ QOL effects of CT decision

Thank you