Biomarker Data 101

OR

Bridging the Transdisciplinary Communication Gap

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Information about SSC Accreditation of Professional Statisticians at http://www.ssc.ca/en/accreditation

Overview of Talk

1. What is a biomarker?
2. Biomarker use.
3. Breast cancer biomarker assessments.
4. Sources of biomarker assay variability.
5. Case studies.
6. Work in progress.

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What is a biomarker?

NIH (Environmental Health Sciences):
"Biomarkers are key molecular or cellular events that link a specific environmental exposure to a health outcome."

NCI:
"A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease."

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Biomarker Use

1. Risk of developing disease.
2. Diagnosis.
3. Response to therapy: success, toxicity.
4. Risk of sequelae: same/other disease, death.

➔**Tension/tradeoff for actionable targets/therapy**

Biomarker data (mostly measured, continuous)

vs

Frequently-assessed for action (categorical).

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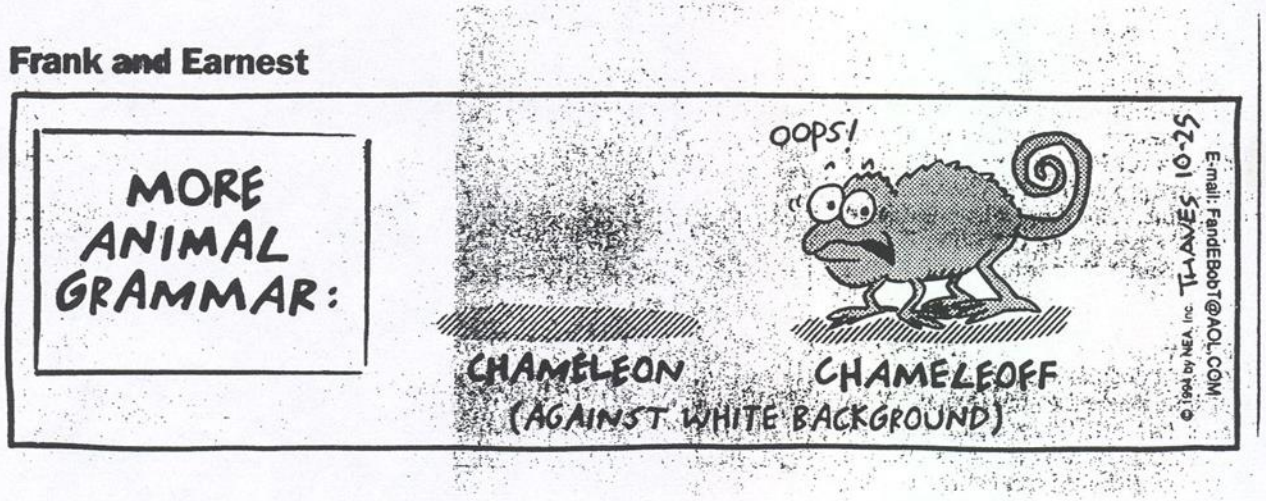
DECISION THEORY



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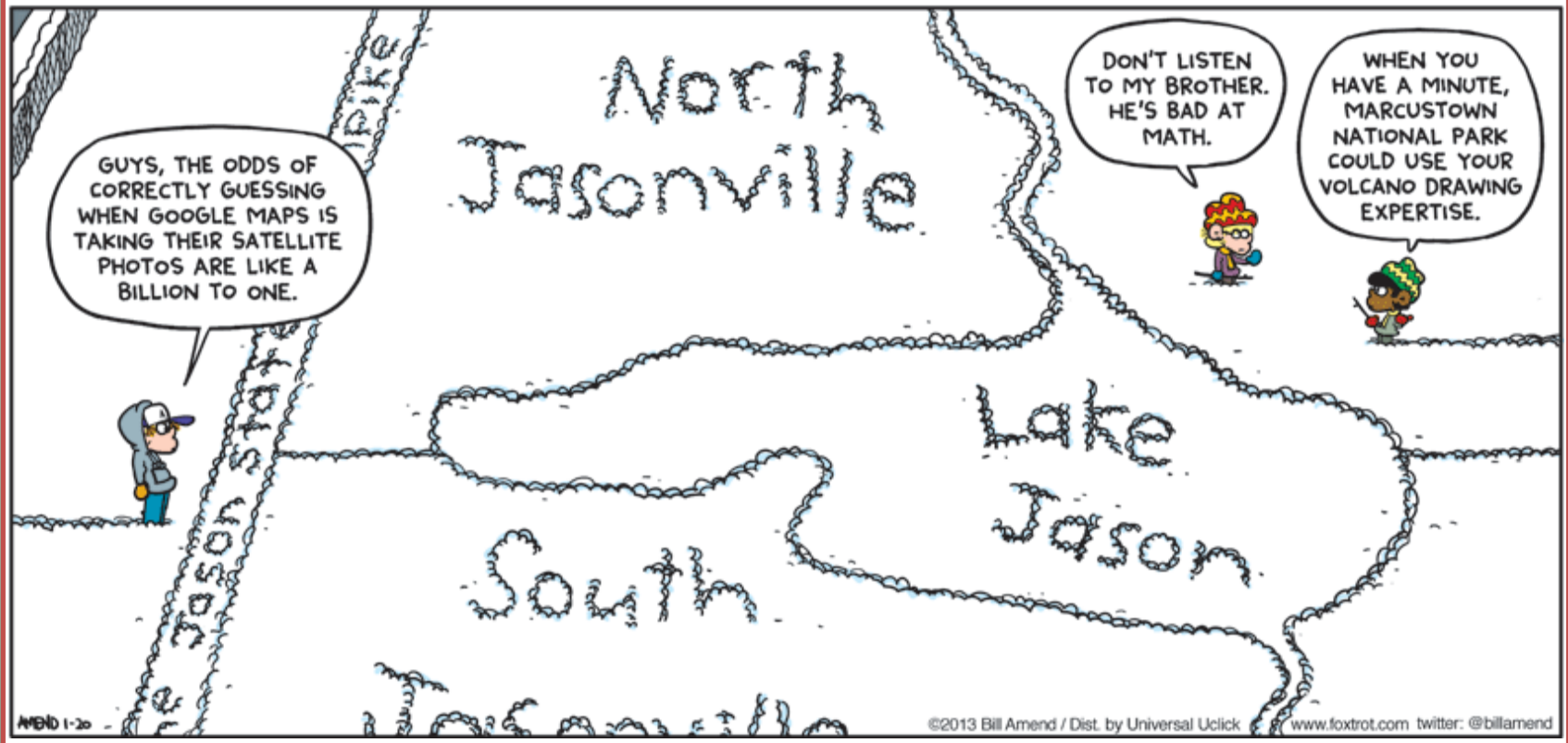
Chance of hitting the right cut-point(s) for clinical action?



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Breast Cancer Biomarker Assessments

1. **Determinant of endocrine therapy**:

Up to 20% of immunohistochemical (IHC) Estrogen Receptor (ER) and Progesterone Receptor (PR) inaccurate:

ASCO/CAP IHC Guidelines (Hammond MEH, et al. J Clin Oncol 2010)

➔ ER+, PR+ with ≥ 1% cells staining;

➔ Establishment of more external quality assurance programs.

2. **Determinant of anti-HER2 therapy:**

Up to 20% of human epidermal growth factor receptor 2 (HER2) gene inaccurate:

ASCO/CAP Guidelines (Wolff AC, et al. J Clin Oncol 2007; 2012)

➔ Establishment of cut-points;

➔ Establishment of more external quality assurance programs.

3. **Ki67 Working Group:**

NIH moratorium on using banked Breast Cancer trial specimens to assess ki67: (Dowsett M, et al. J Natl Cancer Inst 2011)

➔ Work in progress (Lisa McShane involved as statistician)

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Sources of Biomarker Assay Variability

Kananaskis Working Group:

Assessing genetic markers of tumour progression in the context of intratumour heterogeneity.

Chapman JW, Wolman E, Wolman SR,…

Shankey TV. Cytometry 1998; 31:67-73.

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Quantification of Heterogeneity

Assessed tumour heterogeneity encompasses:

1. Reproducibility error;
2. Intratumour heterogeneity, which may change in a tumour with time
   - Not routinely assessed;
3. Intertumour differences among tumours.

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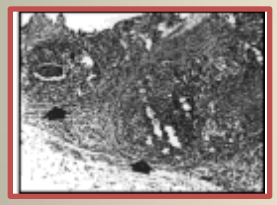
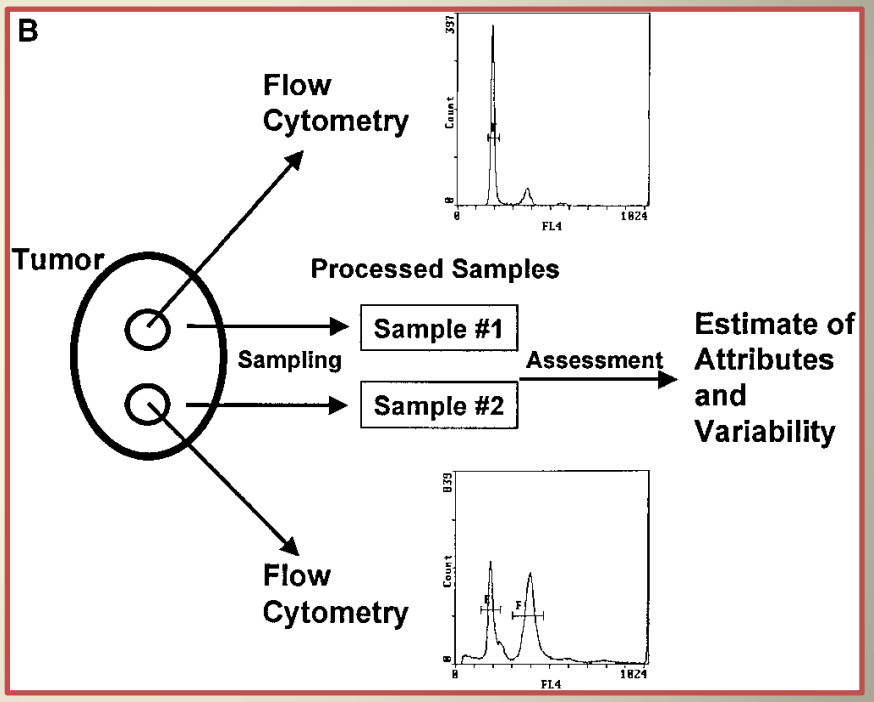
Demonstrated Tumour Heterogeneity





Courtesy of Vince Shankey [Chapman JW,…,Shankey TV. Cytometry 31:67–73 (1998)

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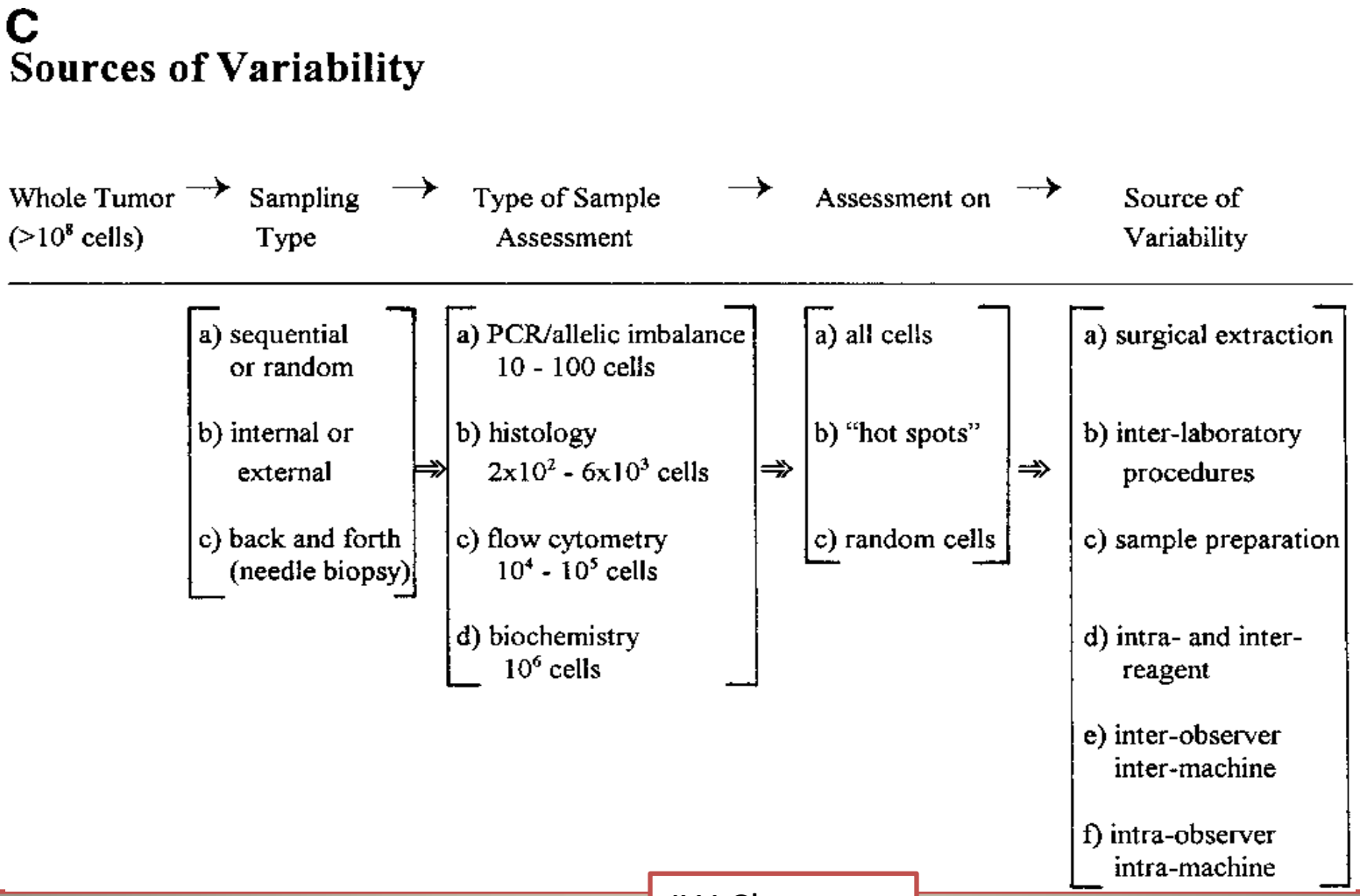
Underlying Tumour Heterogeneity:

Chapman, et al [Cytometry 31:67–73 (1998)]



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Pragmatic Handling of Different Methods, Sample Sizes (# of cells), Variability

- ➔ Currently, assume + is +, different assays.
- ➔ Assume measuring similar process(es).
- ➔ Expect differences in location/scale.
- ➔ Where possible, investigate using multivariable, continuous biomarker data:

(Kananaskis Working Group, Cytometry 1998;

REMARK 2012, BMC Medicine 2012, 10:51
Altman DG, McShane LM, Sauerbrei W,
Taube SE)

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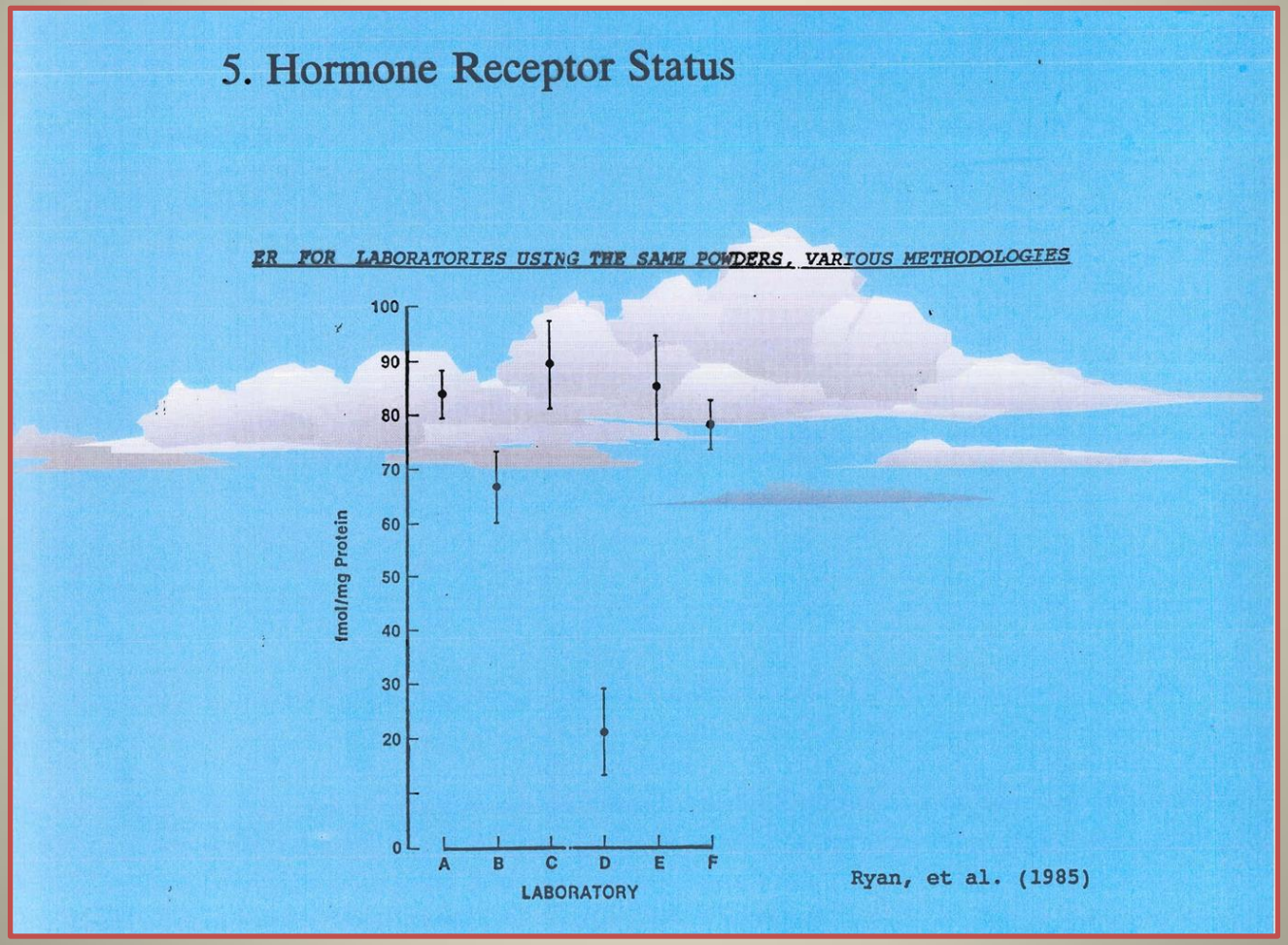
Case Study: Biochemical Dextran-Coated Charcoal (DCC; Radioligand binding) Assay for ER



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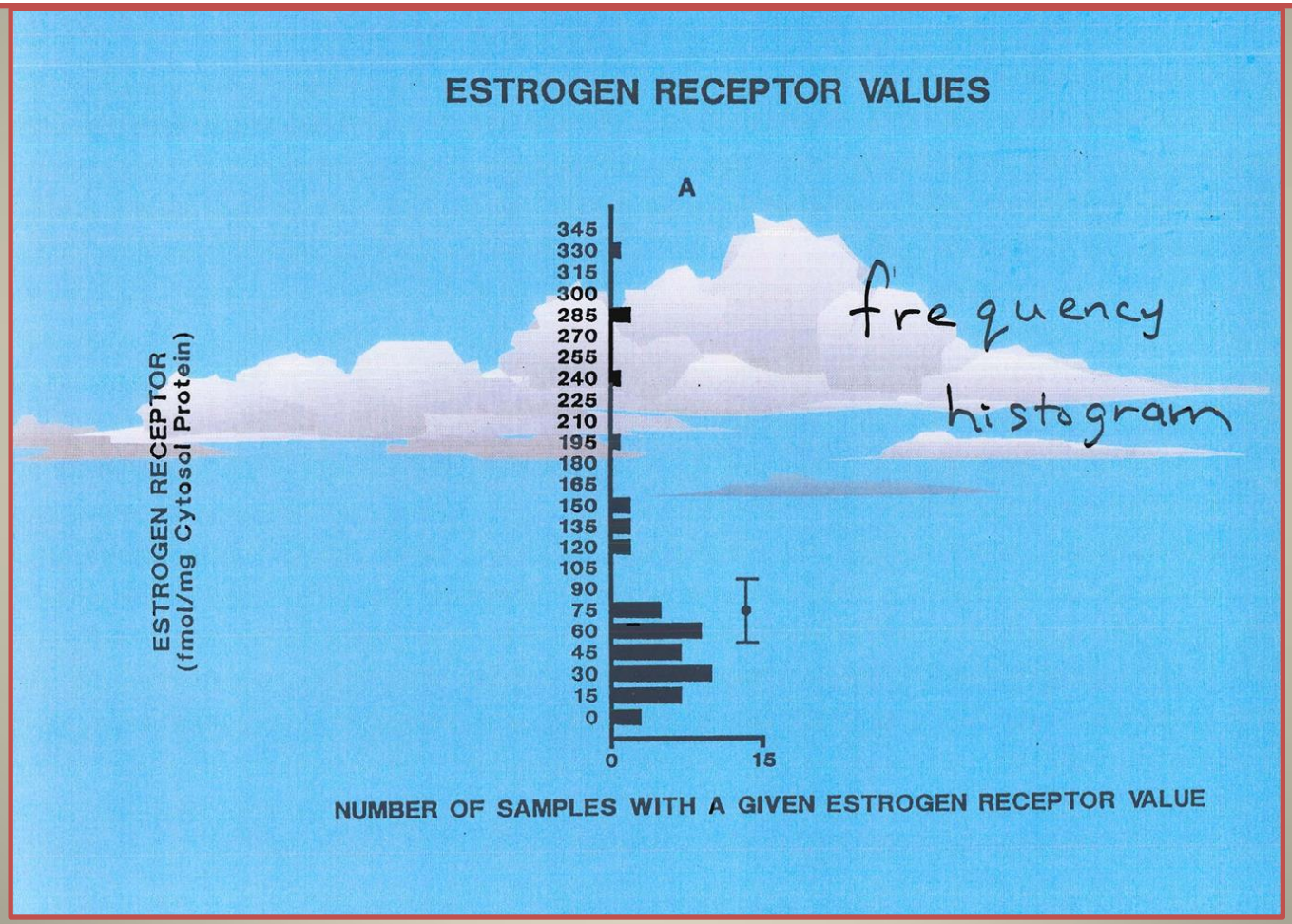
ER Frequency Histogram: Laboratory A



Chapman JW, Mobbs BG, et al. J Steroid Biochem Molec Biol 1993; 45:367-373.

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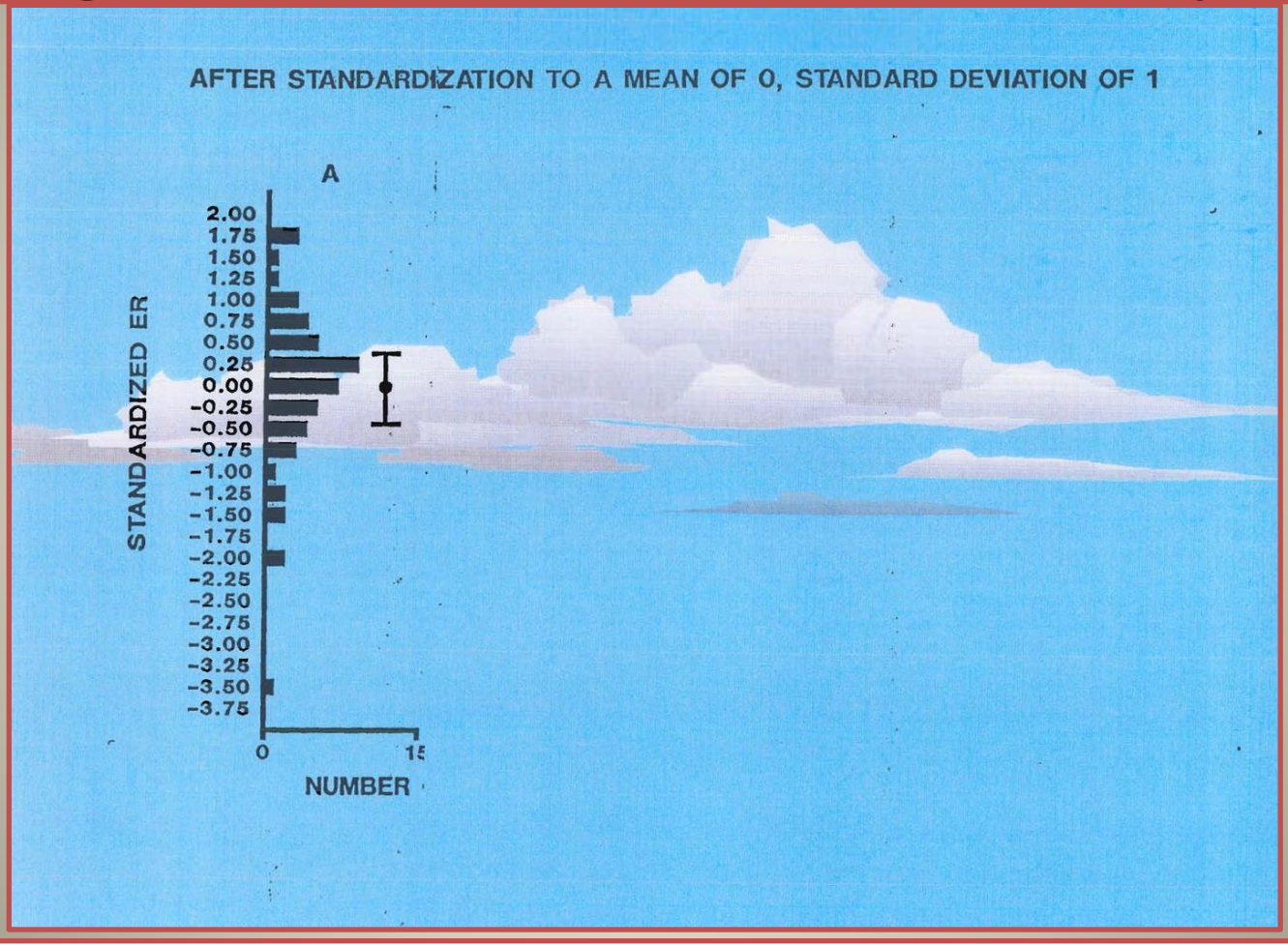
Statistically Standardized Logarithim (ER) for Laboratory A



Chapman JW, Mobbs BG, et al. J Steroid Biochem Molec Biol 1993; 45:367-373.

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Comparison of Statistically Standardized ER by Laboratory

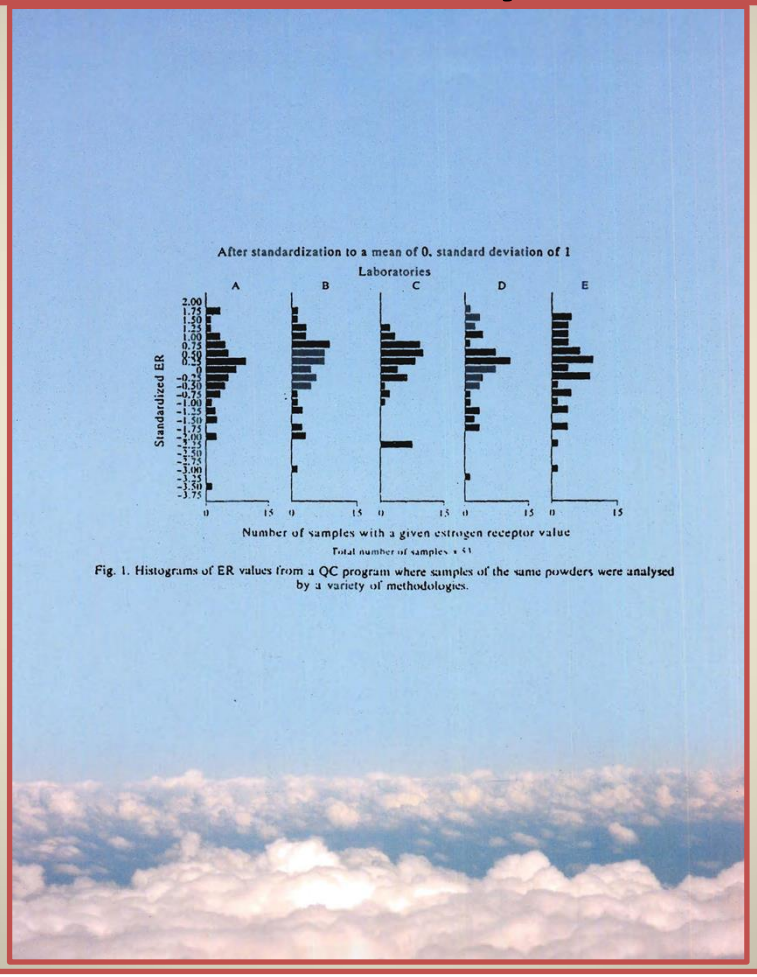

Fig. 1. Histograms of ER values from a QC program where samples of the same powders were analysed by a variety of methodologies.

Chapman JW, Mobbs BG, et al. J Steroid Biochem Molec Biol 1993; 45:367-373.

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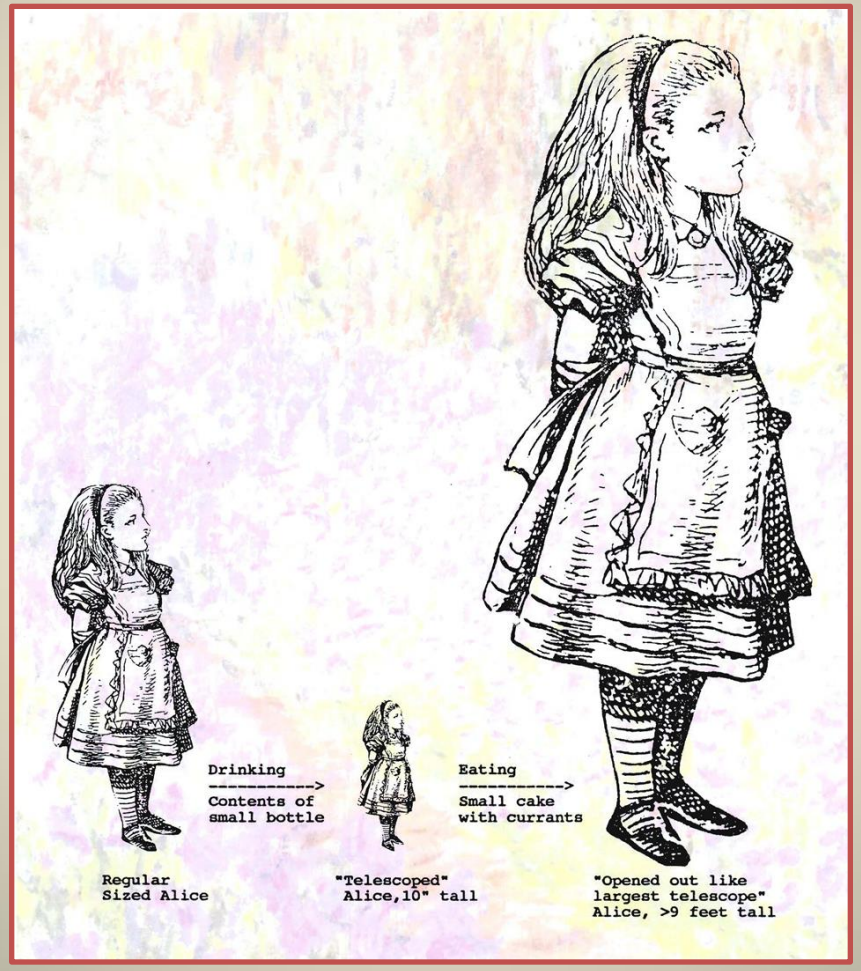
Double 1 to 1 Transformation



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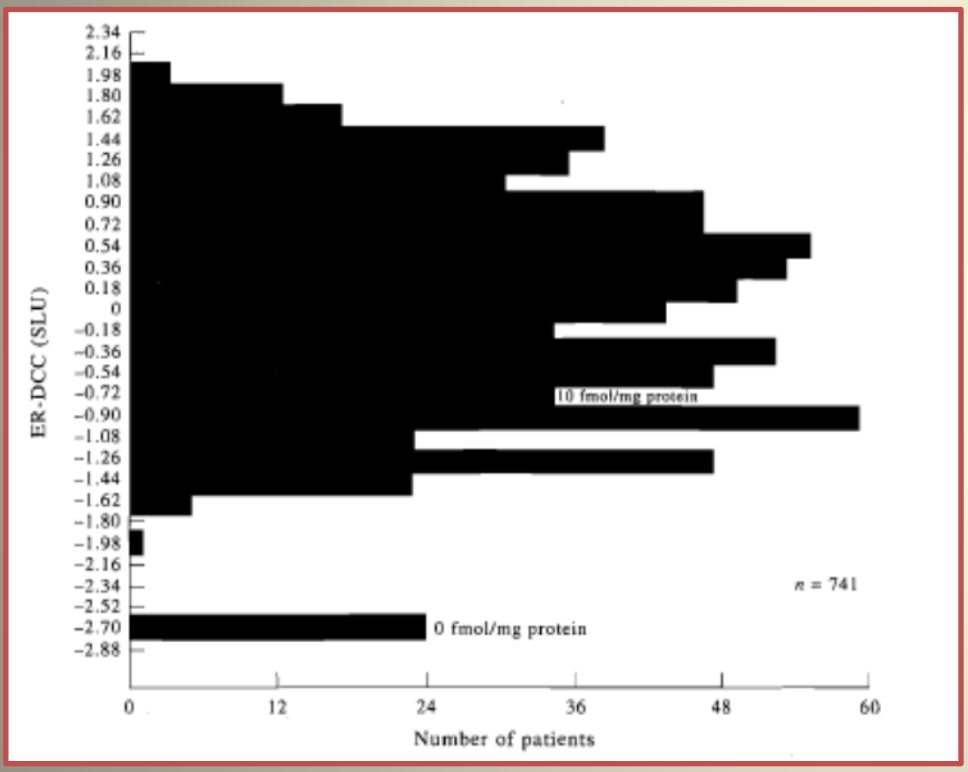
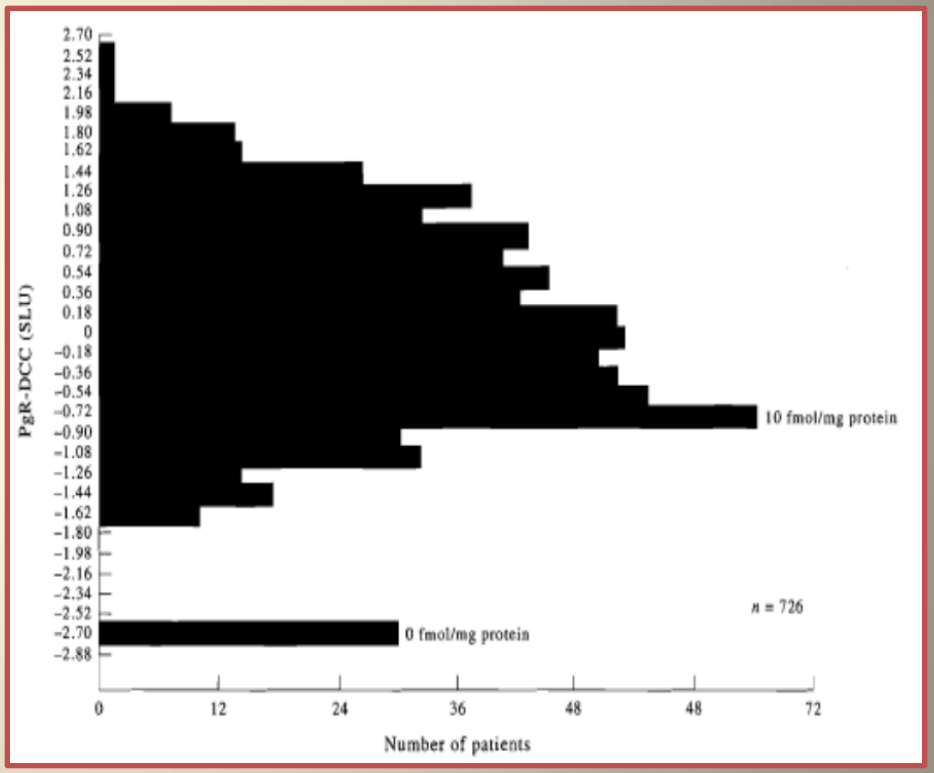
Frequency Histograms of ER-DCC in Standardized Log Units (SLU)





Chapman JW, Mobbs BG, et al, Eur J Cancer, 1996)

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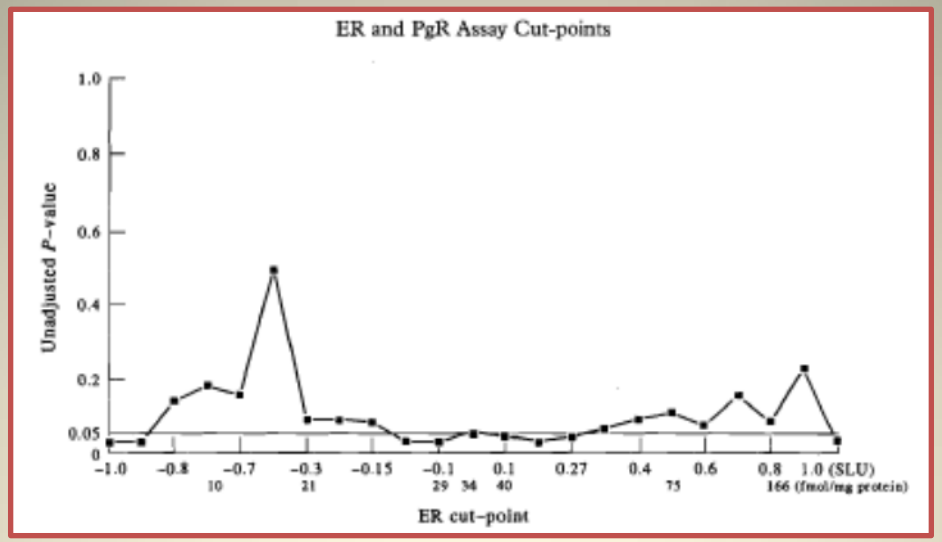

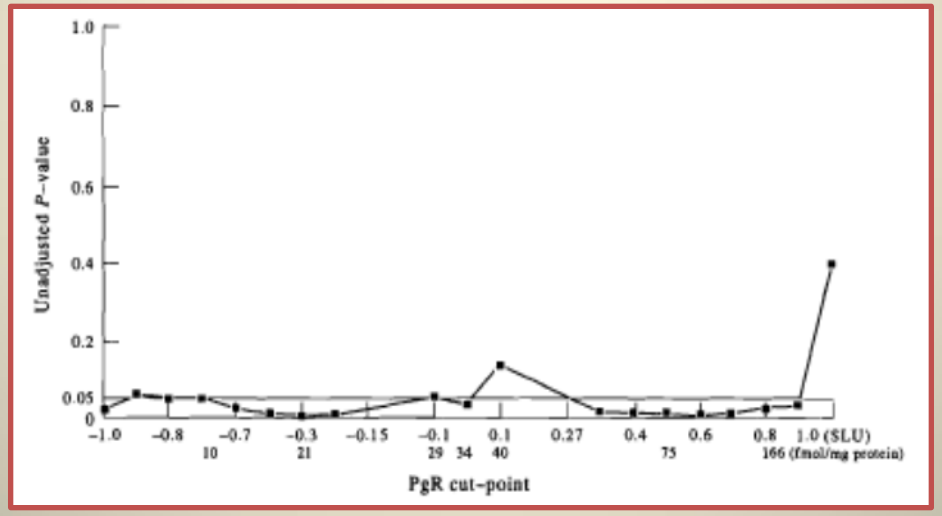

Chapman JW, Mobbs BG, et al. J Steroid Biochem Molec Biol 1996; 57:323-328.

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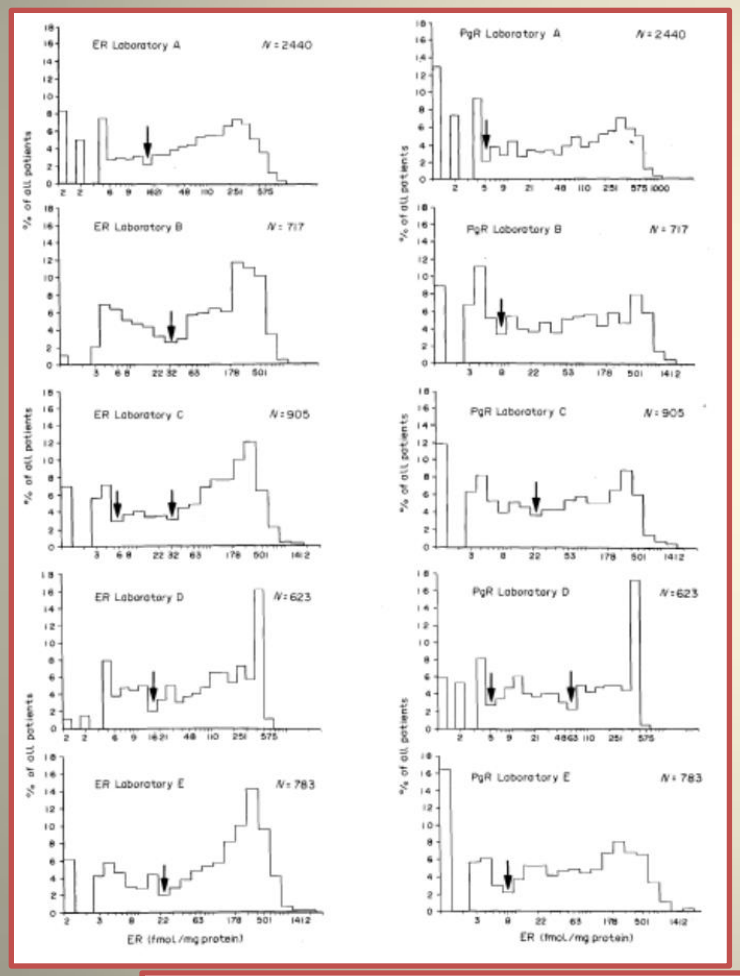
Biochemical ER and PR by Enzymeimmunoassay (EIA; double monoclonal antibody)



One conclusion in paper, about bimodality:
"It is conceivable that oestradiol-binding mutant ERs may occur which have altered binding properties for the antibodies used In the EIA."
Postulated existence of ERβ

Mobbs BG, Chapman JW, et al. Eur J Cancer 1993; 29:1292-1297

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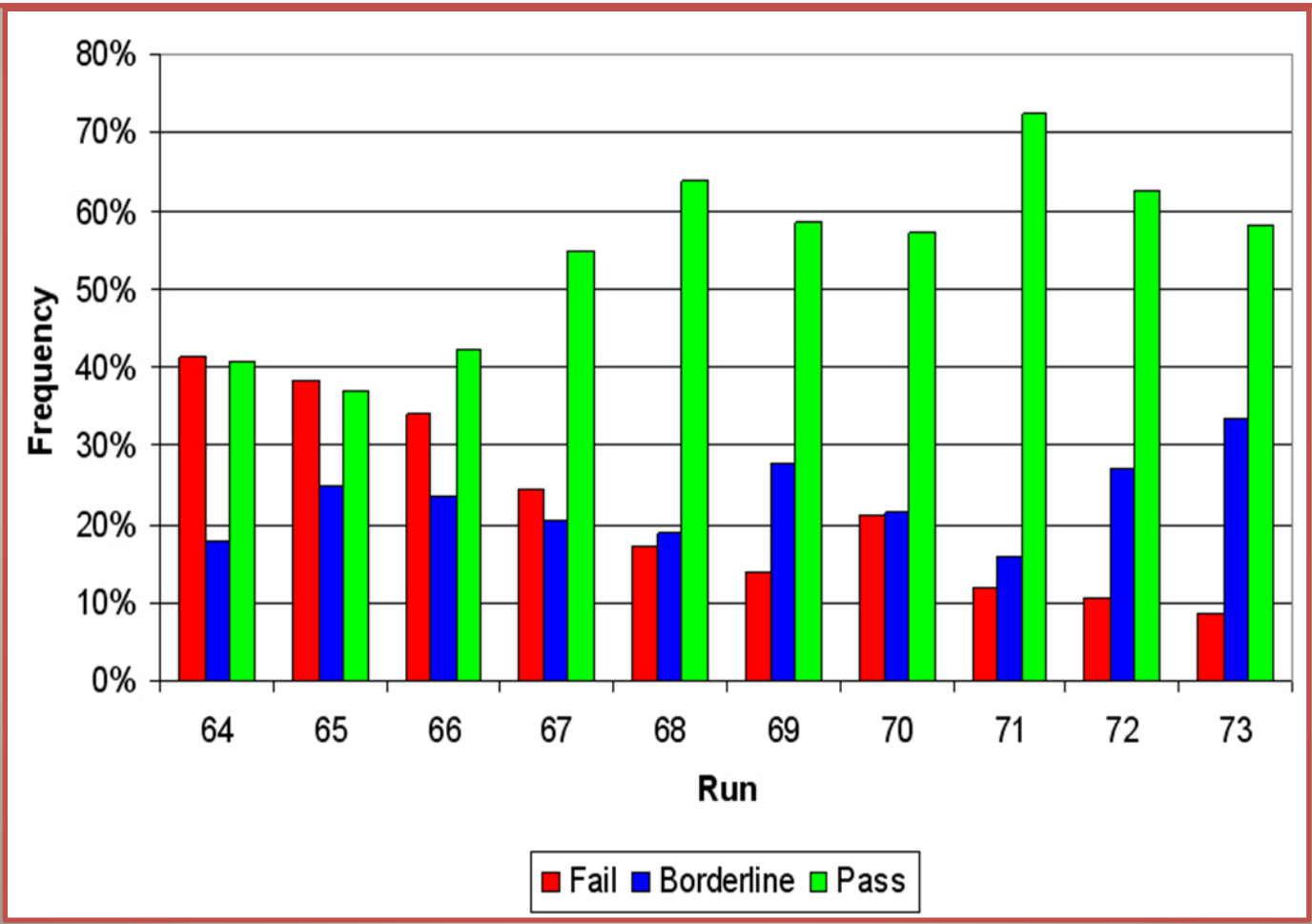
IHC Estrogen Receptor: UK NEQAS ICC & ISH
Courtesy of B Jasani, M Ibrahim, K Miller



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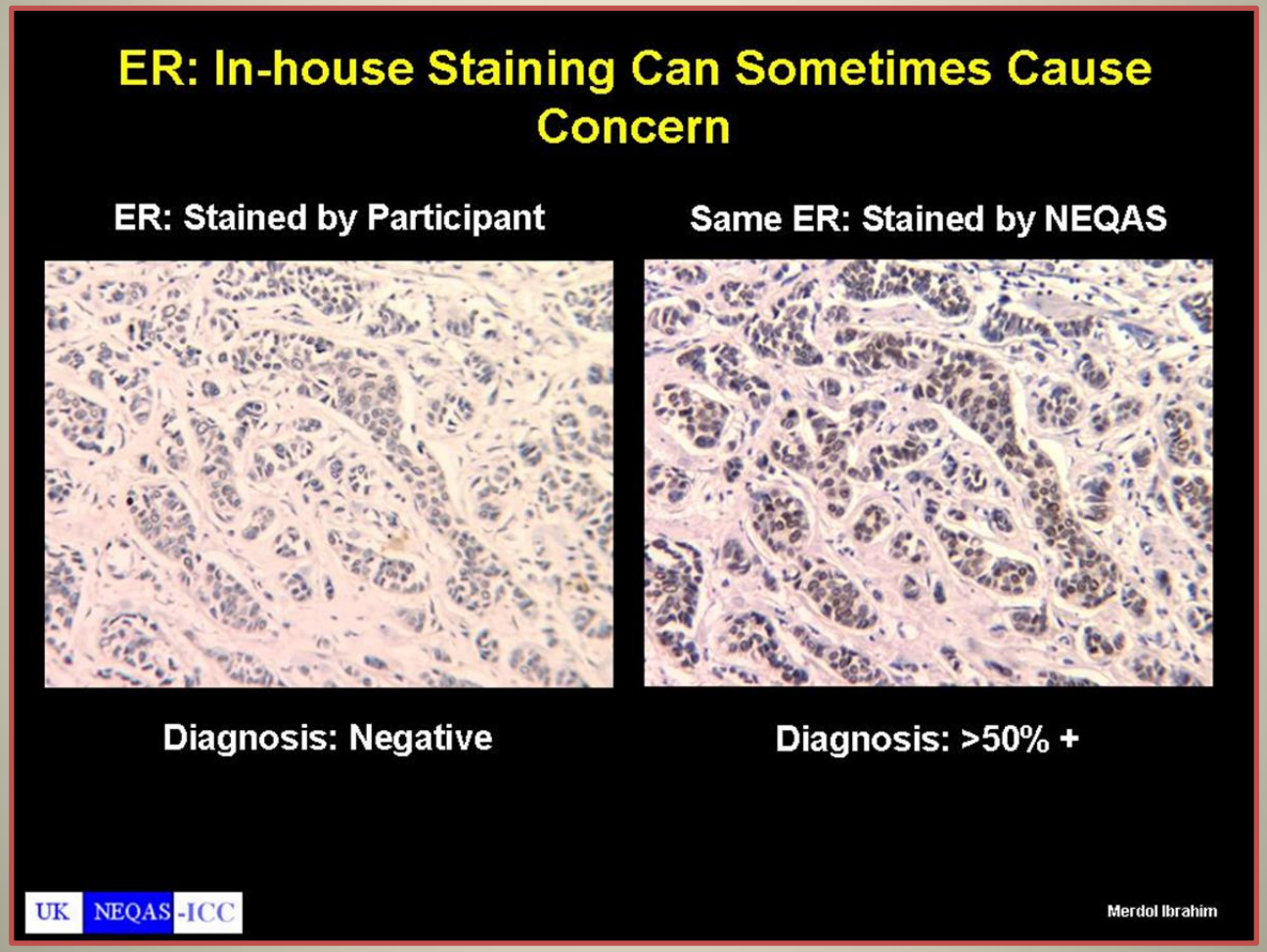
Example of Order of Difference



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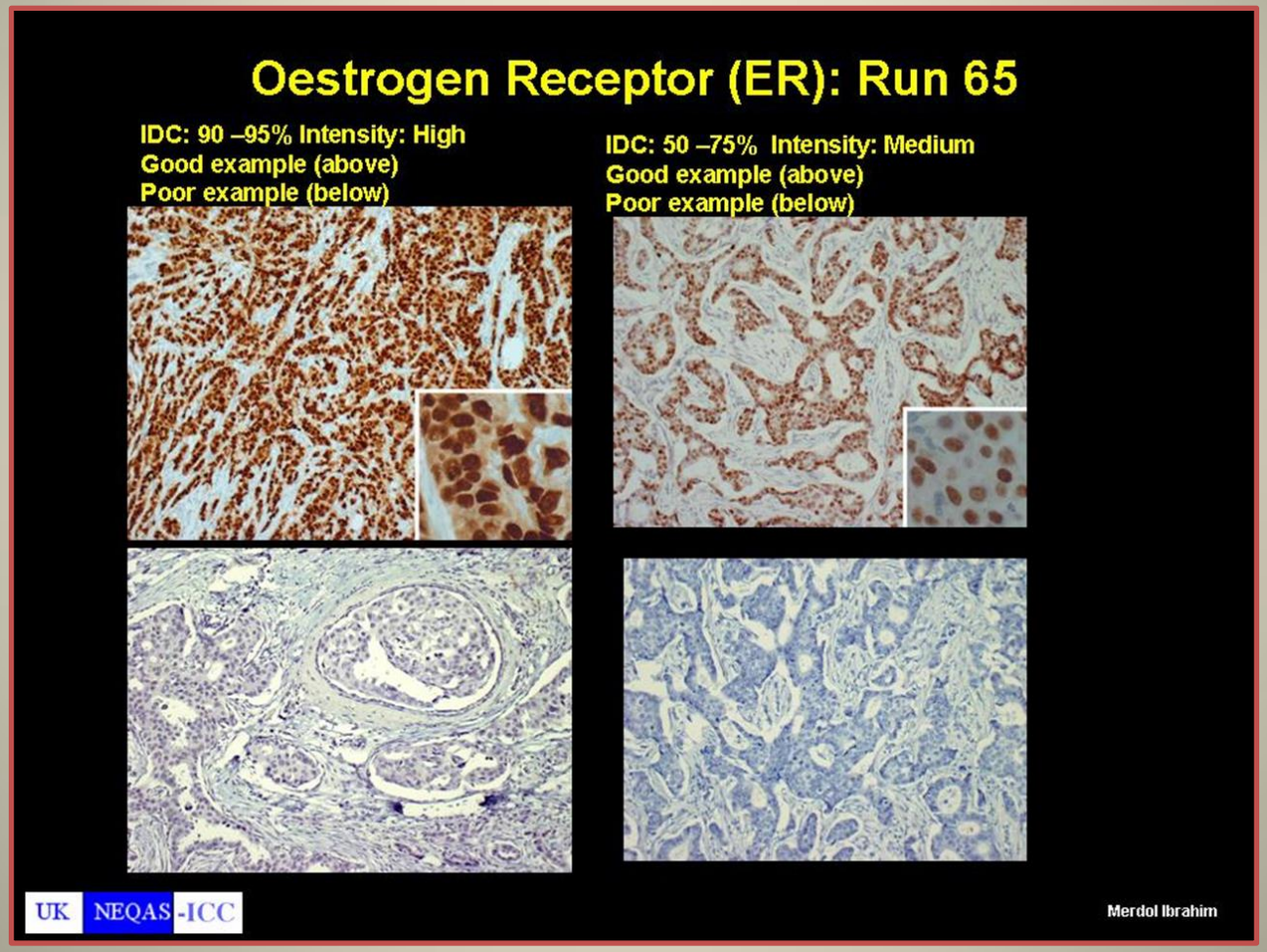
More IHC Examples



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Statistical Standardization

Akin to current World Health Organization mandated

T-scores and Z-scores

for Bone Mineral Density(BMD):

work with standard deviations.

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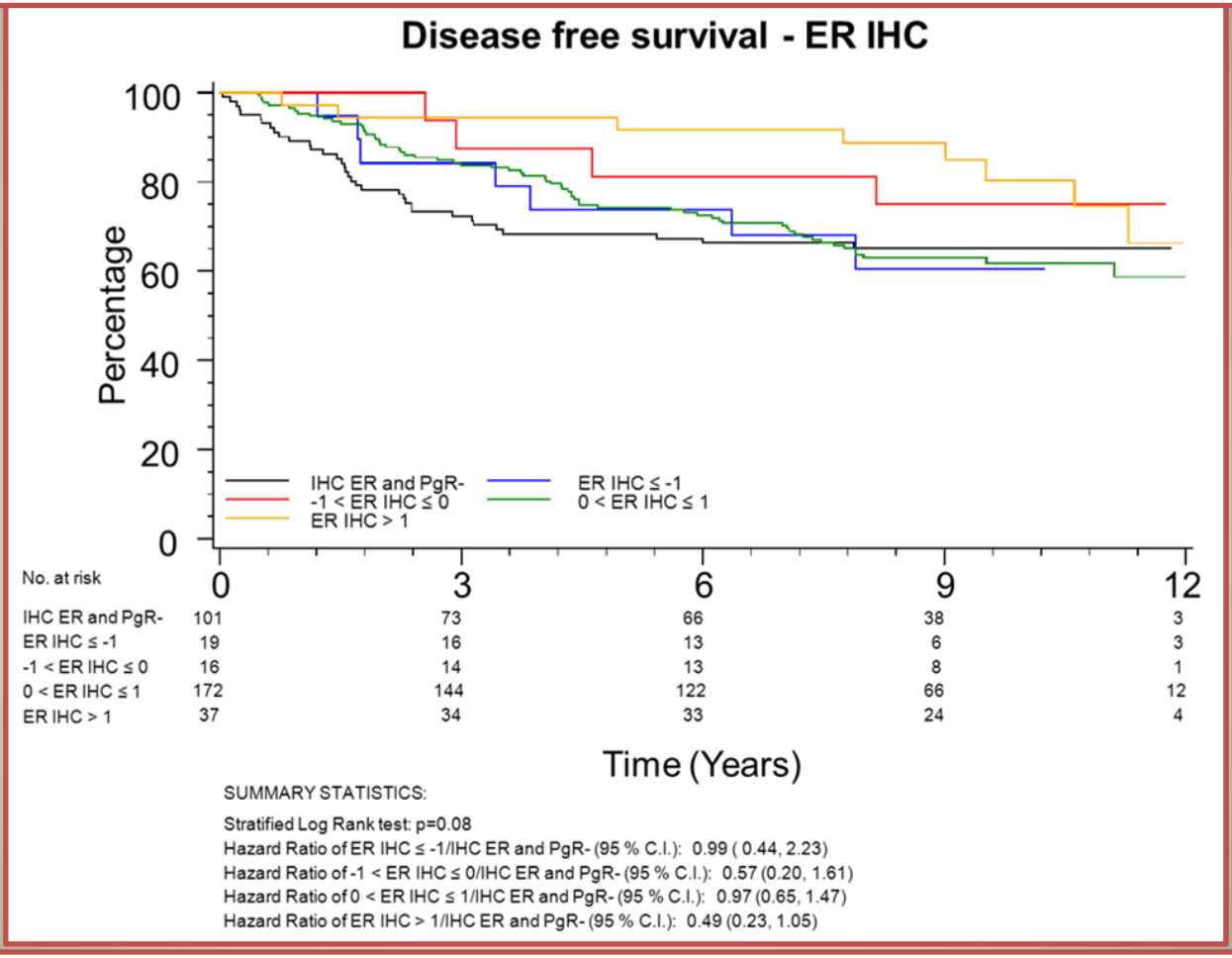
NCIC CTG MA.12: both ER+/-



Chapman JW, Nielsen TO, et al. Breast Cancer Research 2013; 15:R71

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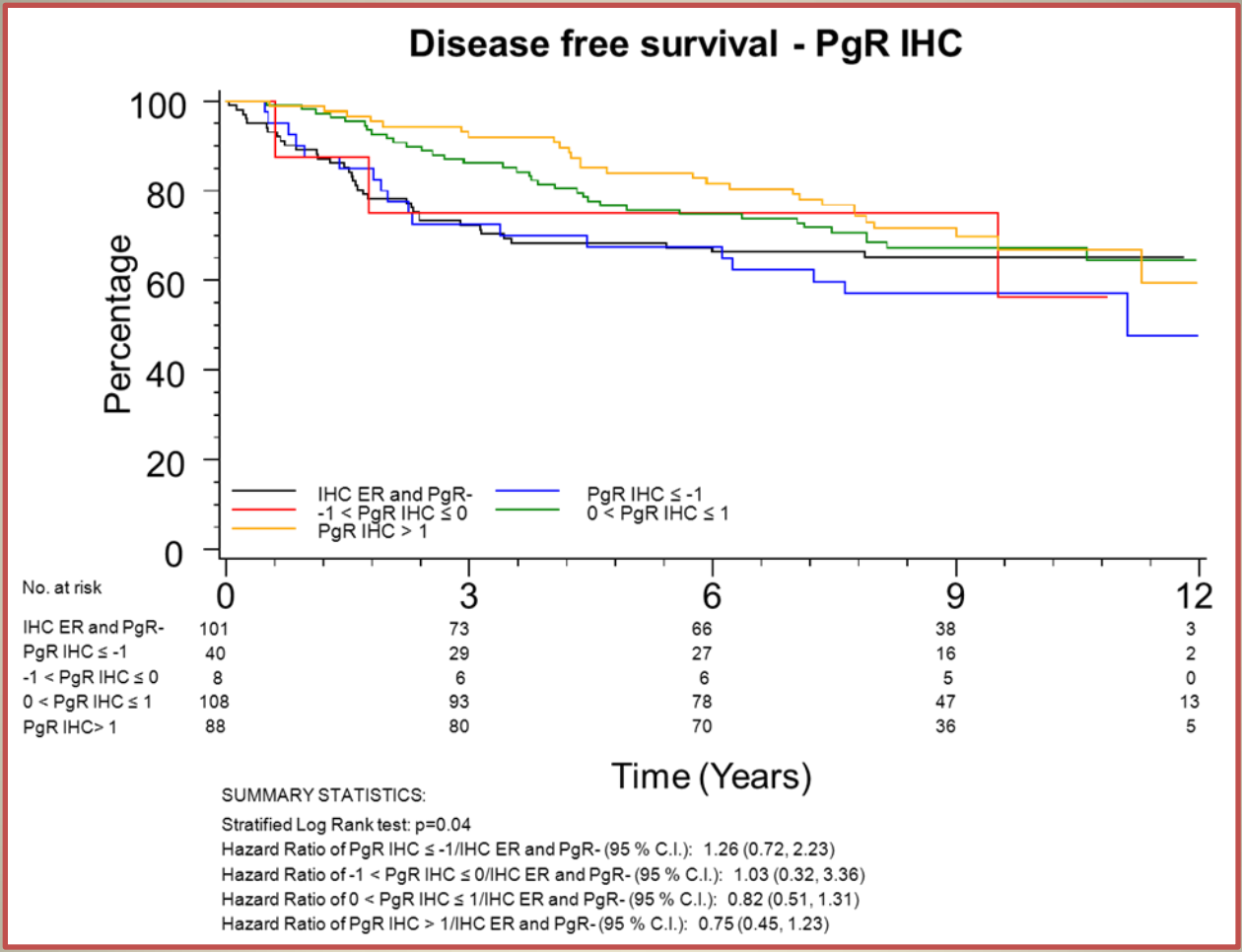

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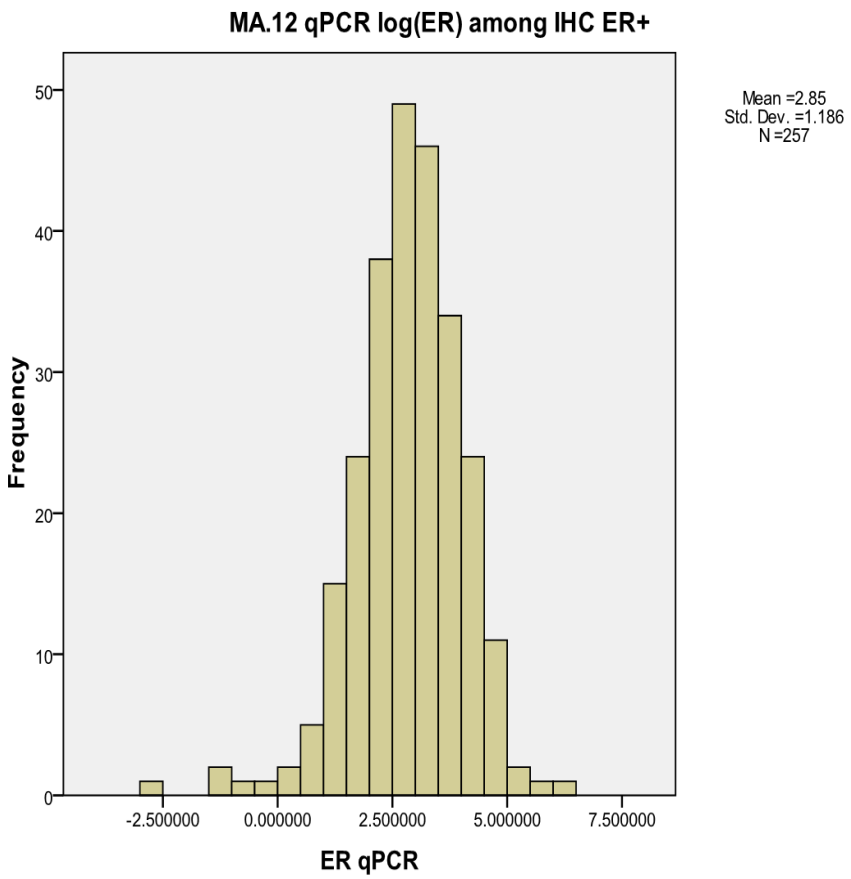

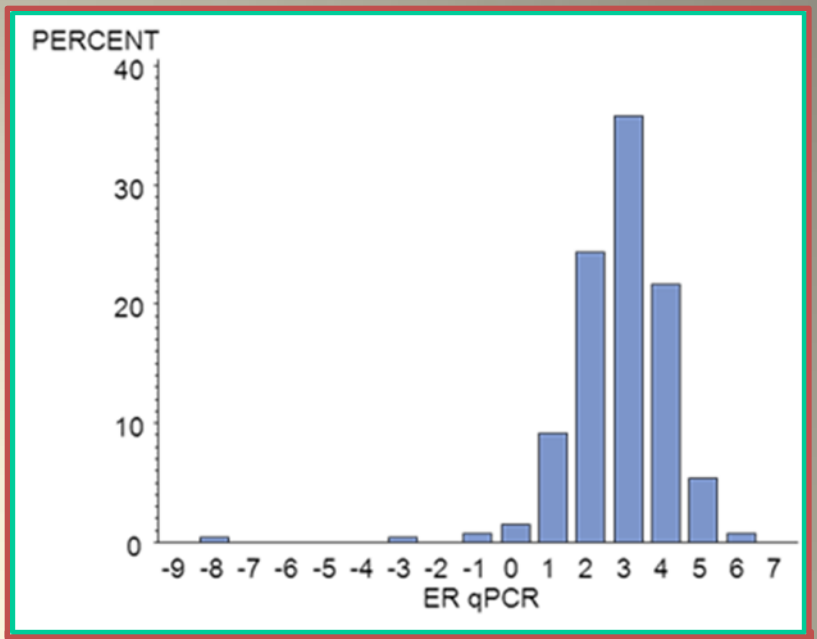

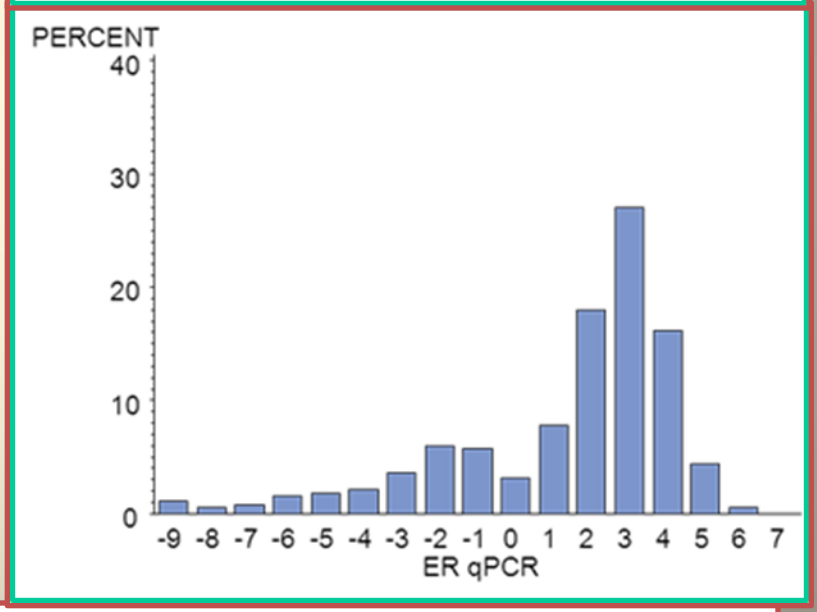

Chapman JW, Nielsen TO, et al. Breast Cancer Research 2013; 15:R71

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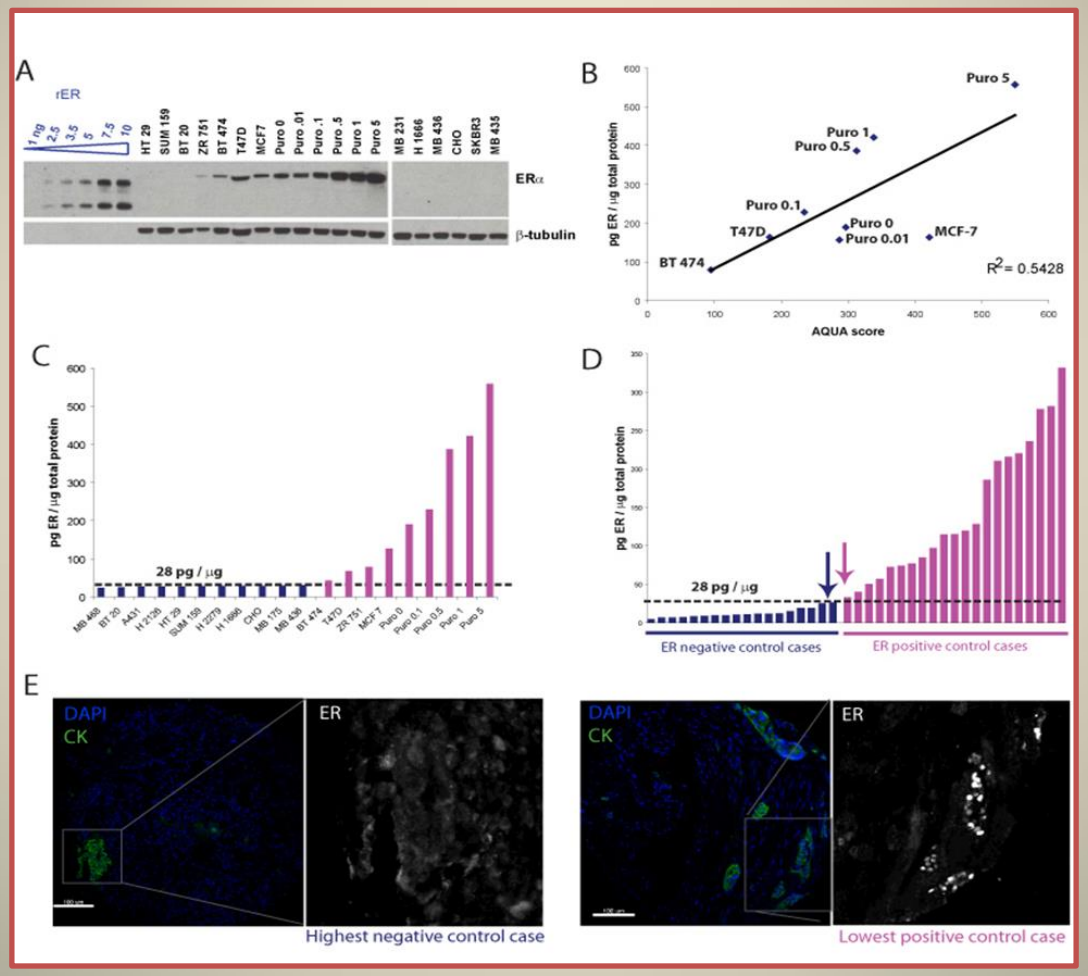
David Rimm's AQUA



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Work in Progress

Statistical standardization of ER, PR, HER2, (ki67) using large NCIC CTG MA.27 trial (exemestane vs anastrozole) tumour samples, clinical follow-up:

with Bharat Jasani, Keith Miller (UCL Advanced Diagnostics),

Paul Goss and Lois Shepherd (MA.27),

Sandip SenGupta (Queen's).

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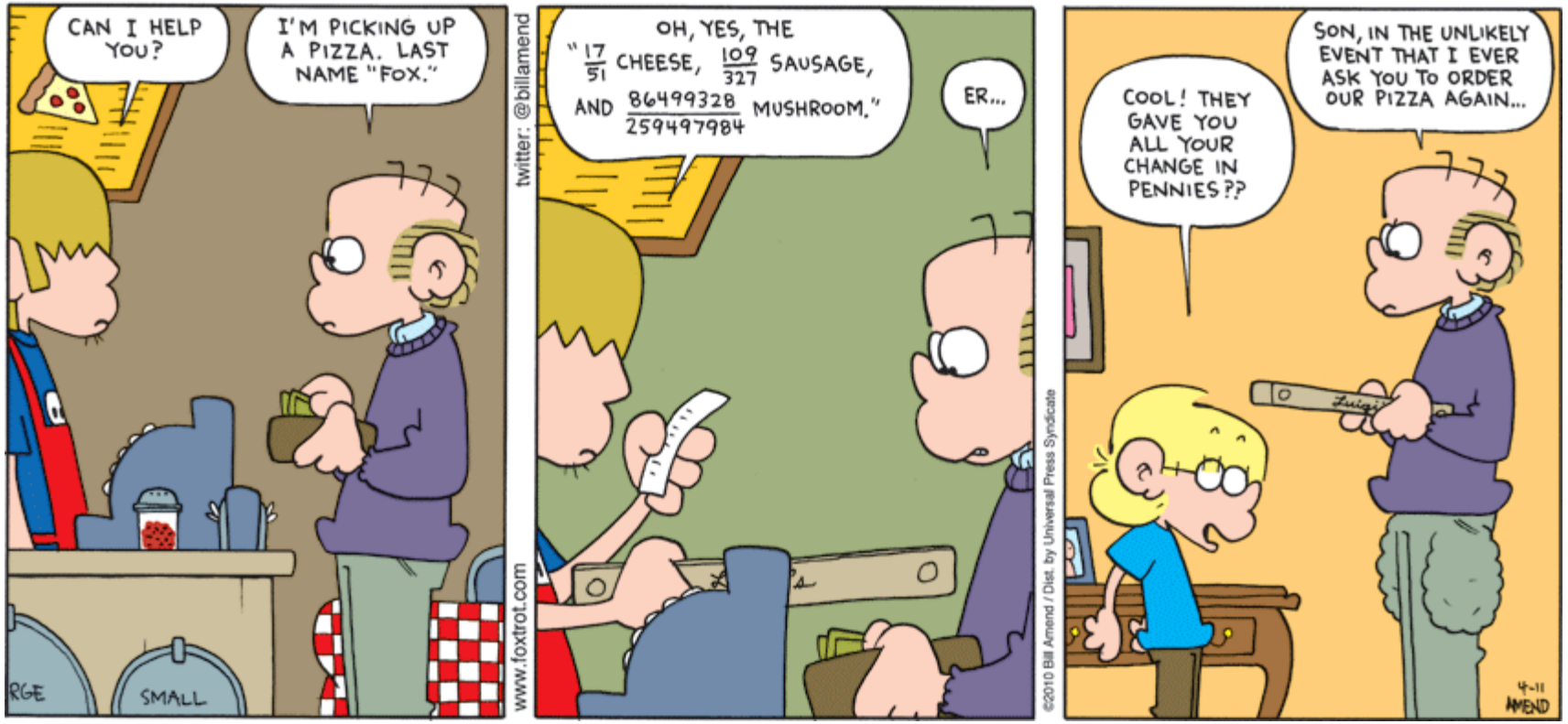
Statistical details at appropriate level for area of practice?



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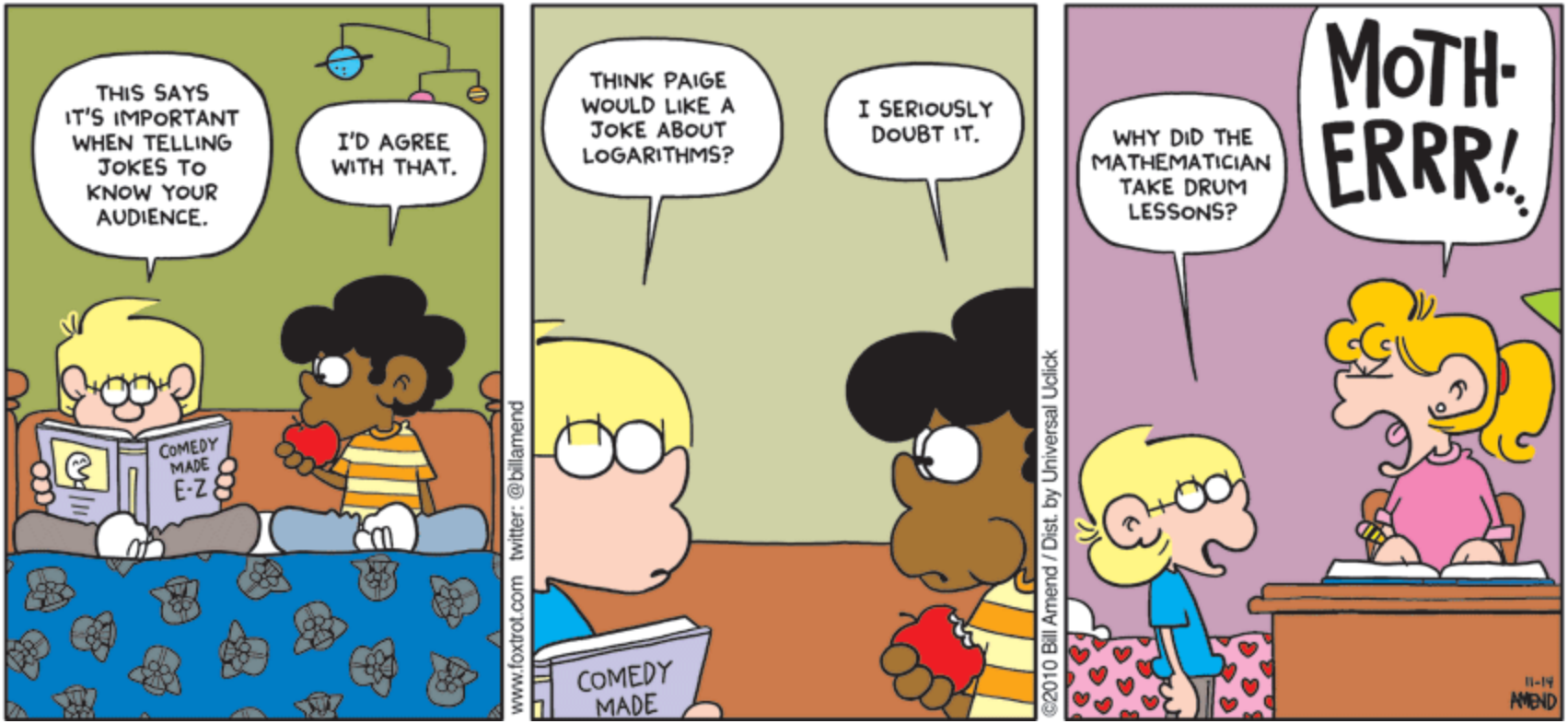
Communicated with good oral and written skills?



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Acknowledgements: mid 1980s➔

- Betty Mobbs, Ontario Biochemical QC group; Betty Mobbs, Lavina Lickley, Kathy Pritchard, David McCready, Maureen Trudeau, Henrietta Banting Breast Centre (HBBC) group; David Murray, St. Michael's hospital (s-phase of HBBC tumours).
- Kananaskis Working Group, particularly Vince Shankey, Eric and Sandra Wolman.
- NCIC CTG MA.12: Torsten Nielsen, Vivien Bramwell, Lois Shepherd.
- NCIC CTG MA.14: Dennis Sgroi, Paul Goss, Michael Pollak, Lois Shepherd.
- UK NEQAS/UCL Advanced Diagnostics Bharat Jasani, Keith Miller; NCIC CTG MA.27 Paul Goss, Lois Shepherd; Sandip SenGupta (Queen's University).
- Patients who consented to use of their tumours and clinical follow-up for research purposes.

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