

Systems approaches: A Copernican revolution in the cancer-centric universe.



Stefano Bonassi, PhD
Clinical and Molecular Epidemiology
IRCCS San Raffaele Pisana, Rome - Italy



San Raffaele S.p.A.

The Copernican Revolution

In 1543 Nicolas Copernicus published his treatise *De Revolutionibus Orbium Coelestium* (The Revolution of Celestial Spheres) where a new view of the world is presented: the heliocentric model.



All the reassurances of the cosmology of the Middle Ages were gone, and a new view of the world, less secure and comfortable, came into being.

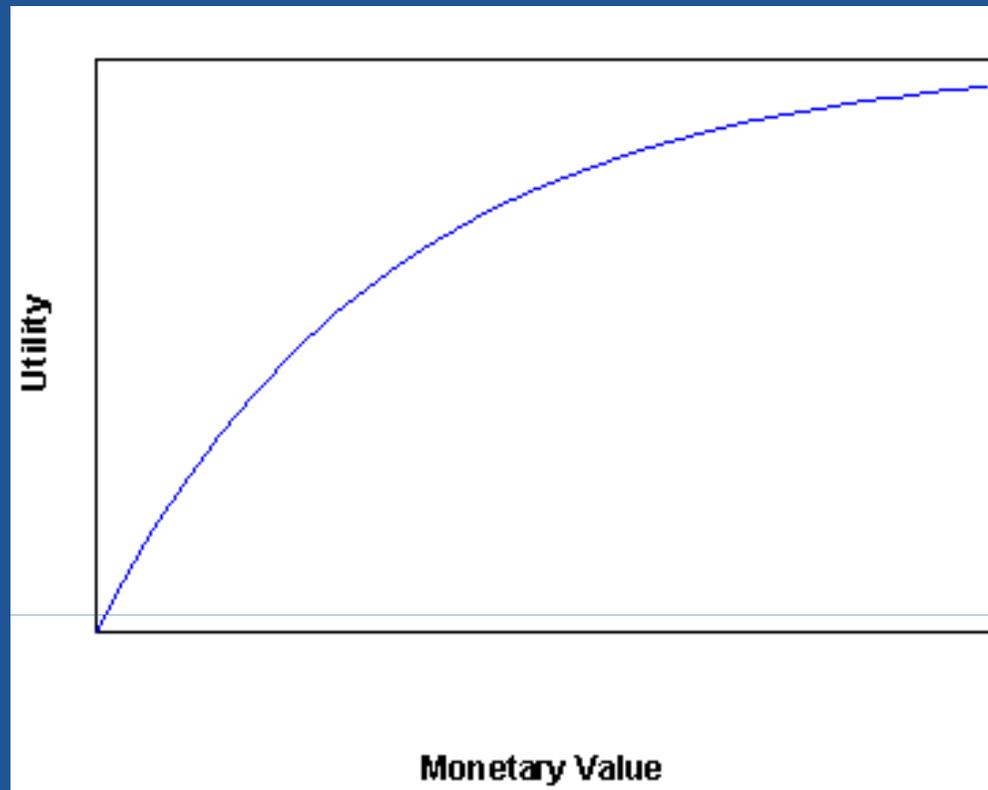
Copernicus, Nicholas (1473-1543)



The phrase is now widely used, particularly in the humanities, for a change of perspective, connoting a progressive shift

David Luban has analysed four different sides of the metaphorical usage, deriving from different aspects of the Copernican Revolution as it is understood in the history of science, and its wider impact on thought:

- a sense of uprootedness within cosmology;
- a way of representing the path of reason and Enlightenment;
- mistrust of common sense as a guide to truth;
- a world-picture based on scientific laws rather than narratives.

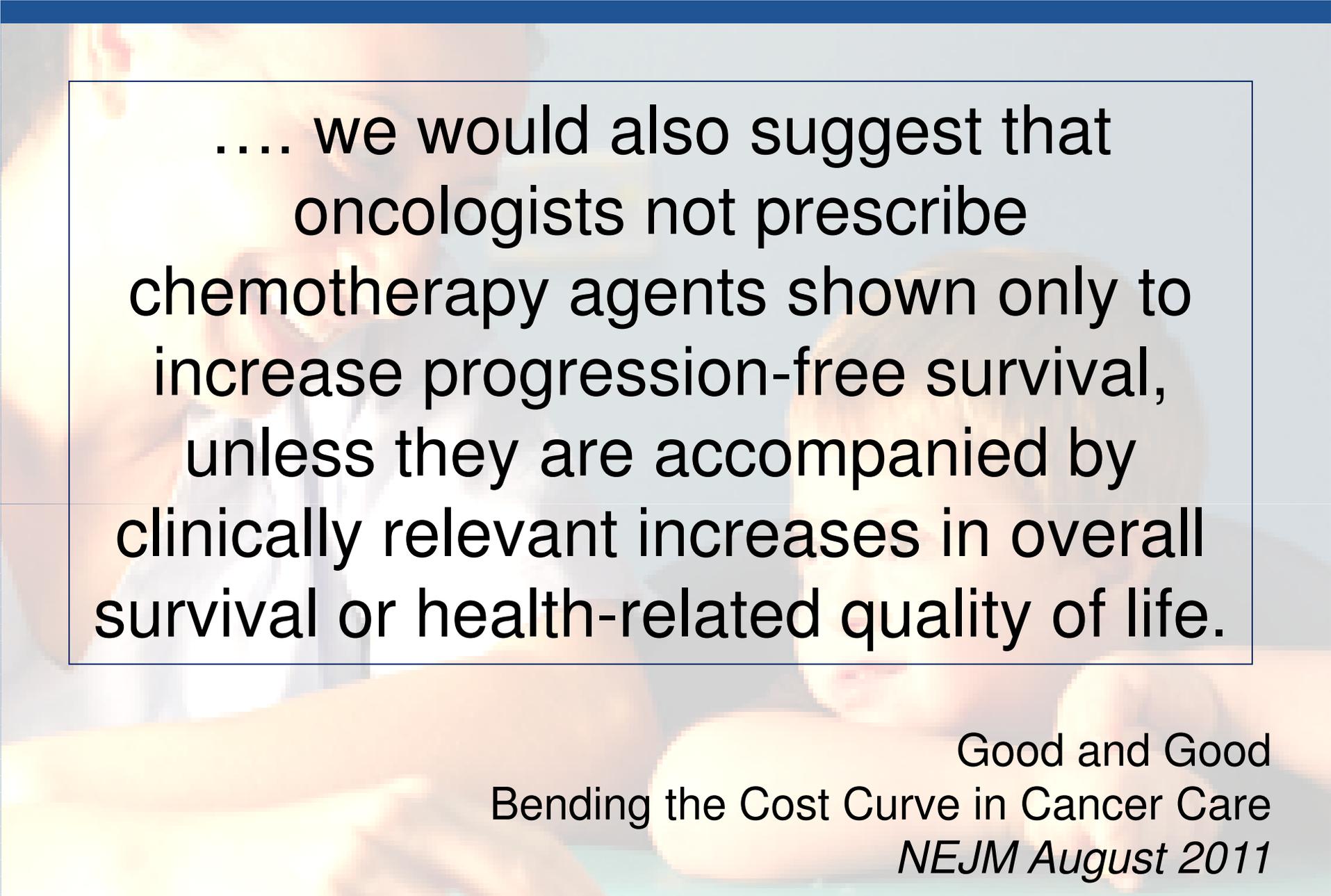


Progressive (and not sustainable) increase of costs paralleled by a limited impact on treatment endpoints

The burden of cancer is growing, and the disease is becoming a major economic expenditure for all developed countries. In 2008, the worldwide cost of cancer due to premature death and disability (not including direct medical costs) was estimated to be US\$895 billion.

The cancer profession and industry should take responsibility and not accept a substandard evidence base and an ethos of very small benefit at whatever cost; rather, we need delivery of fair prices and real value from new technologies

Sullivan R. (and other 37 oncologists from King's College, London, UK)
Delivering affordable cancer care in high-income countries
Lancet Oncol. 2011 Sep;12(10):933-80.



..... we would also suggest that oncologists not prescribe chemotherapy agents shown only to increase progression-free survival, unless they are accompanied by clinically relevant increases in overall survival or health-related quality of life.

Good and Good
Bending the Cost Curve in Cancer Care
NEJM August 2011

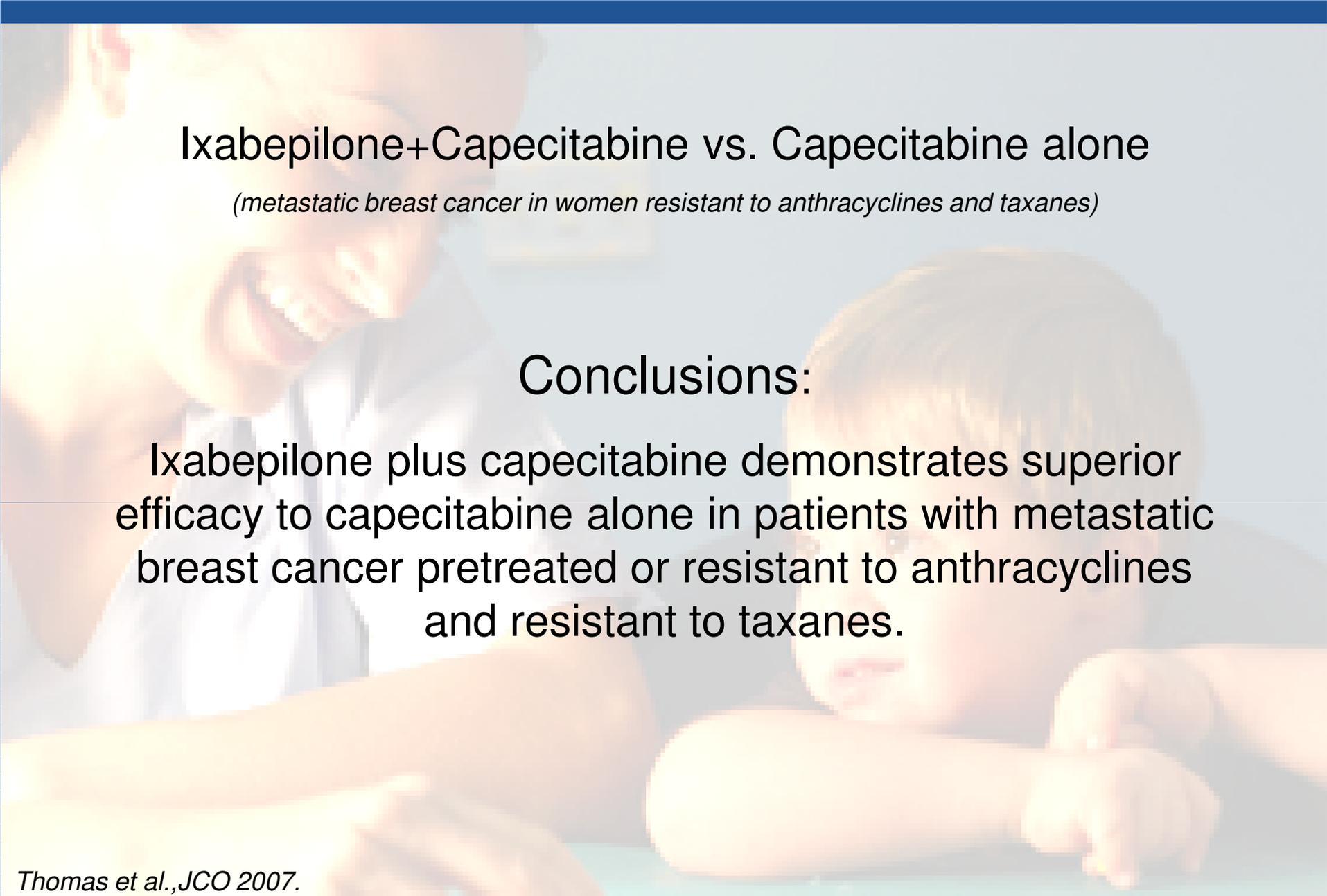
Ixabepilone+Capecitabine vs. Capecitabine alone

(metastatic breast cancer in women resistant to anthracyclines and taxanes)

Results:

- > Progression-free survival ($p < 0.001$)
median: 4.2 vs 5.8
- > Objective response rate ($p < 0.001$)
14% vs 35%
- > Grade 3/4 neuropathy
0% vs 21%
 - > fatigue
3% vs 9%
- > Neutropenia
11% vs 68%
- > Toxicity death rate
1% vs 3%

Thomas et al., JCO 2007.



Ixabepilone+Capecitabine vs. Capecitabine alone

(metastatic breast cancer in women resistant to anthracyclines and taxanes)

Conclusions:

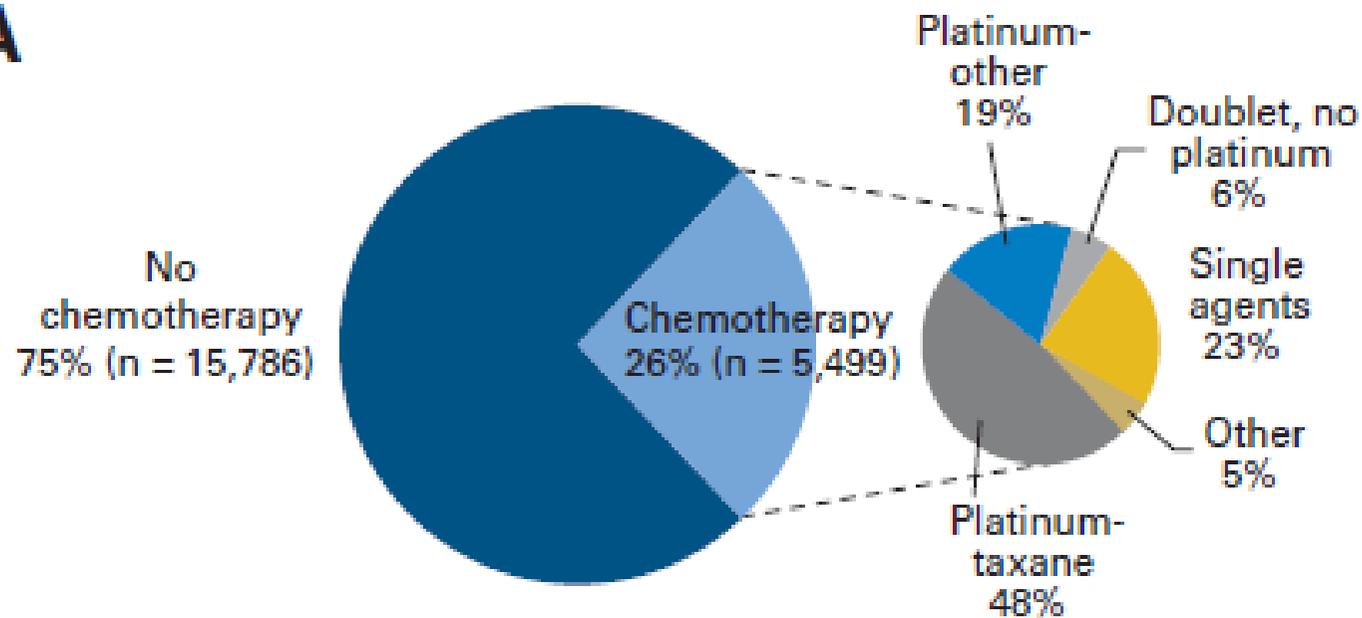
Ixabepilone plus capecitabine demonstrates superior efficacy to capecitabine alone in patients with metastatic breast cancer pretreated or resistant to anthracyclines and resistant to taxanes.

Thomas et al., JCO 2007.

.... Although we accept that any consideration of restricting treatment on the basis of age alone is uncomfortable for many clinicians, we feel that a dialogue regarding the value of treating elderly patients must be initiated.

*Stage III Colon Cancer 84 pts. \pm 80 y (Australia 2003-2010)
Med Surv 2.9 y. 5-years 26.9% 27/46 (58.7%) dying without cancer rec.*

.. considering adjuvant chemotherapy for these patients as exceptional rather than routine

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- SEER Medicare 1997-2002
- Incident AdvNSCLC
- ≥ 66 years

Davidoff et al. JCO, May 2010

Survival Benefit Associated With Chemotherapy Treatments

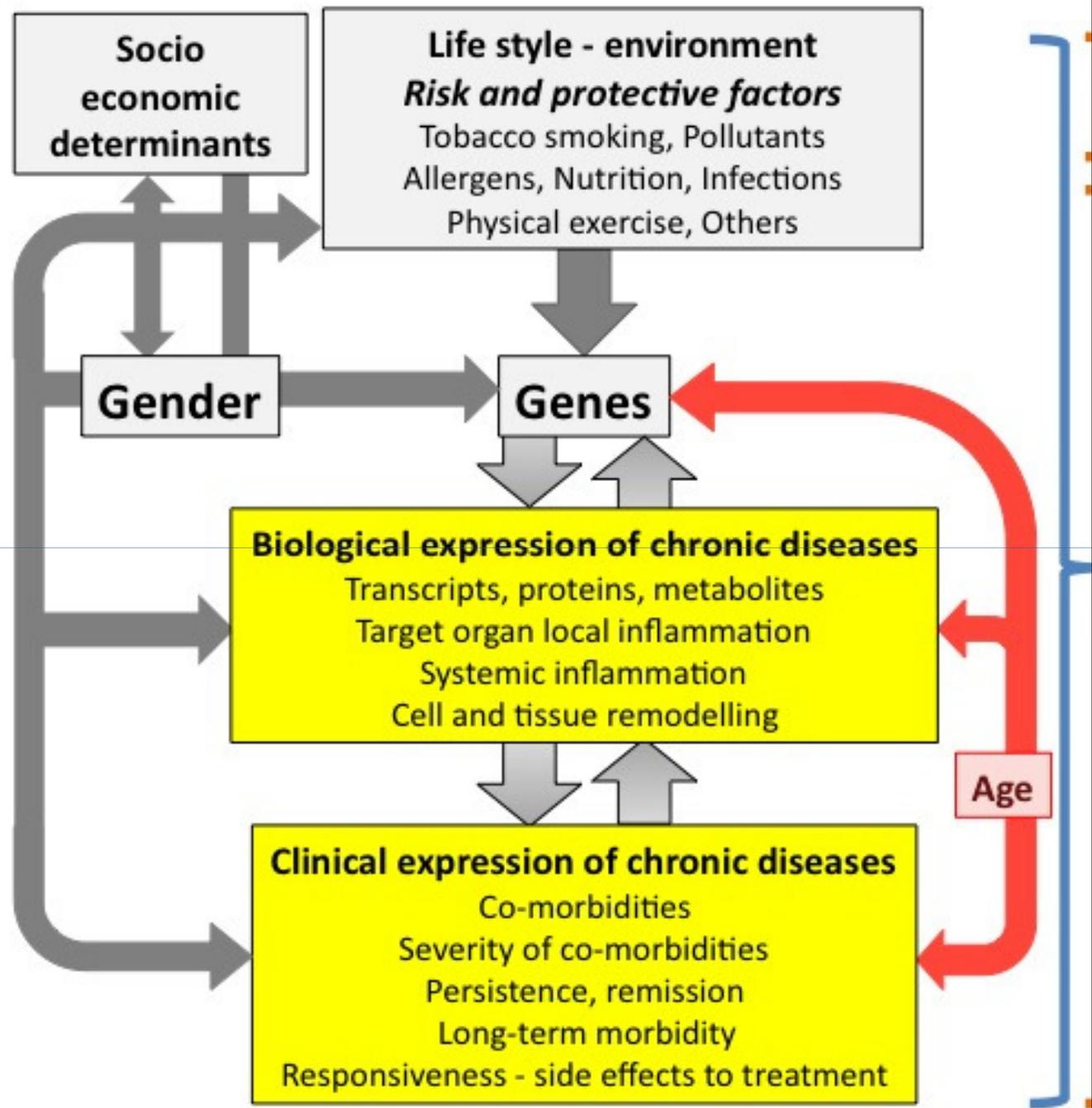
There was a clear survival benefit associated with receipt of some chemotherapy (7.1 v 2.5 months; $P < .001$). Adjusted 1-year survival was 11.6% without (95% CI, 11.1 to 12.0), and 27.0% with chemotherapy (95% CI, 26.4 to 27.6). Among those receiving treatment, median survival was 7.7 months for platinum doublets versus 5.3 months for single agents (Appendix Table A4, online only, provides median survival by chemotherapy receipt and age group.) When we estimated the effects of chemotherapy use on survival duration controlling for patient and disease characteristics, we found that the hazard of death was reduced by approximately one half for treated patients (hazard ratio [HR], 0.558; 95% CI, 0.547 to 0.569;

Comprehensive geriatric assessment (CGA) is a process that consists of a multidimensional data-search and a process of analyzing and linking patient characteristics creating an individualized intervention-plan, carried out by a multidisciplinary team.

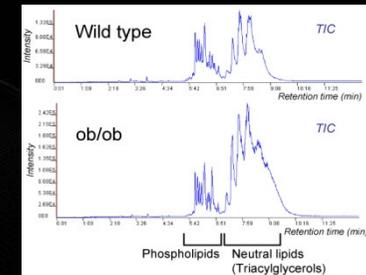
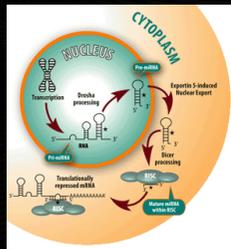
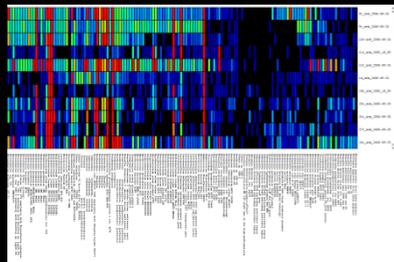
In oncology patients, we reviewed the value of CGA on the following endpoints: recognition of health problems, tolerance to chemotherapy and survival.

The ability of CGA to detect relevant health problems in an elderly population is reported consistently but no randomized studies are available.

So far in oncology there are no prognostic validation studies reported using geriatric syndromes or information based on CGA in its decision making strategies.



- Systems medicine is the application of systems biology to medical research and practice.
- Its objective is to integrate a variety of data at all relevant levels of cellular organization with clinical and patient-reported disease markers, using the power of computational and mathematical modeling, to enable the understanding of the mechanisms, prognosis, diagnosis and treatment of disease.
- Medical informatics will play a key role to structure, integrate and provide access to the enormous amount of data generated.



Gene silencing
Methylation/MiRNA

Metabolism

DNA

Transcription

RNA

Synthesis

Proteins

3M SNPs
Polymorphisms

Gene
expression

Proteome
Millions, coded by 20-30K genes

