Personalized Medicine Coalition

National Pharmaceutical Council

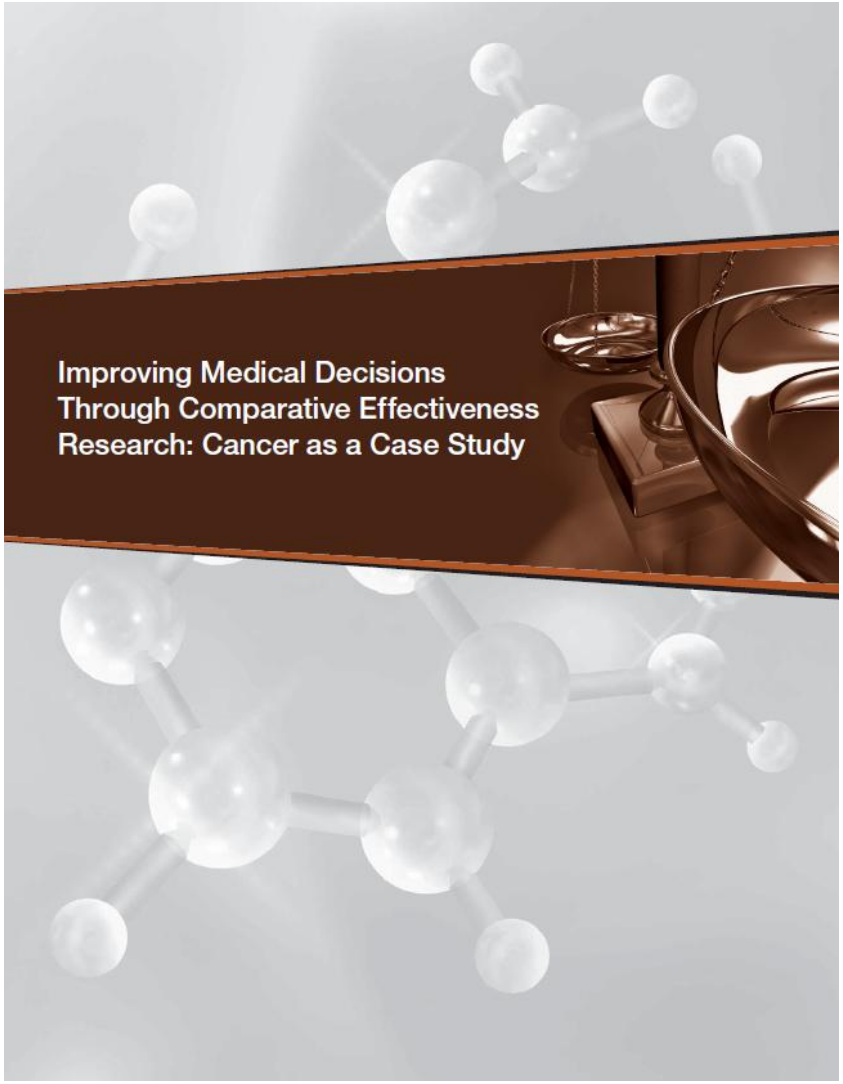
# Comparative Effectiveness Research (CER) and Personalized Medicine: **Policy, Science, and Business**

***How a comprehensive CER system can support personalized medicine***

***Amy P. Abernethy, MD***

***October 28, 2009***

# CER in Cancer Care?



# Friends of Cancer Research Report



## CONTENTS



Improving Medical Decisions Through Comparative Effectiveness Research: Cancer as a Case Study

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# Friends of Cancer Report Recommendations

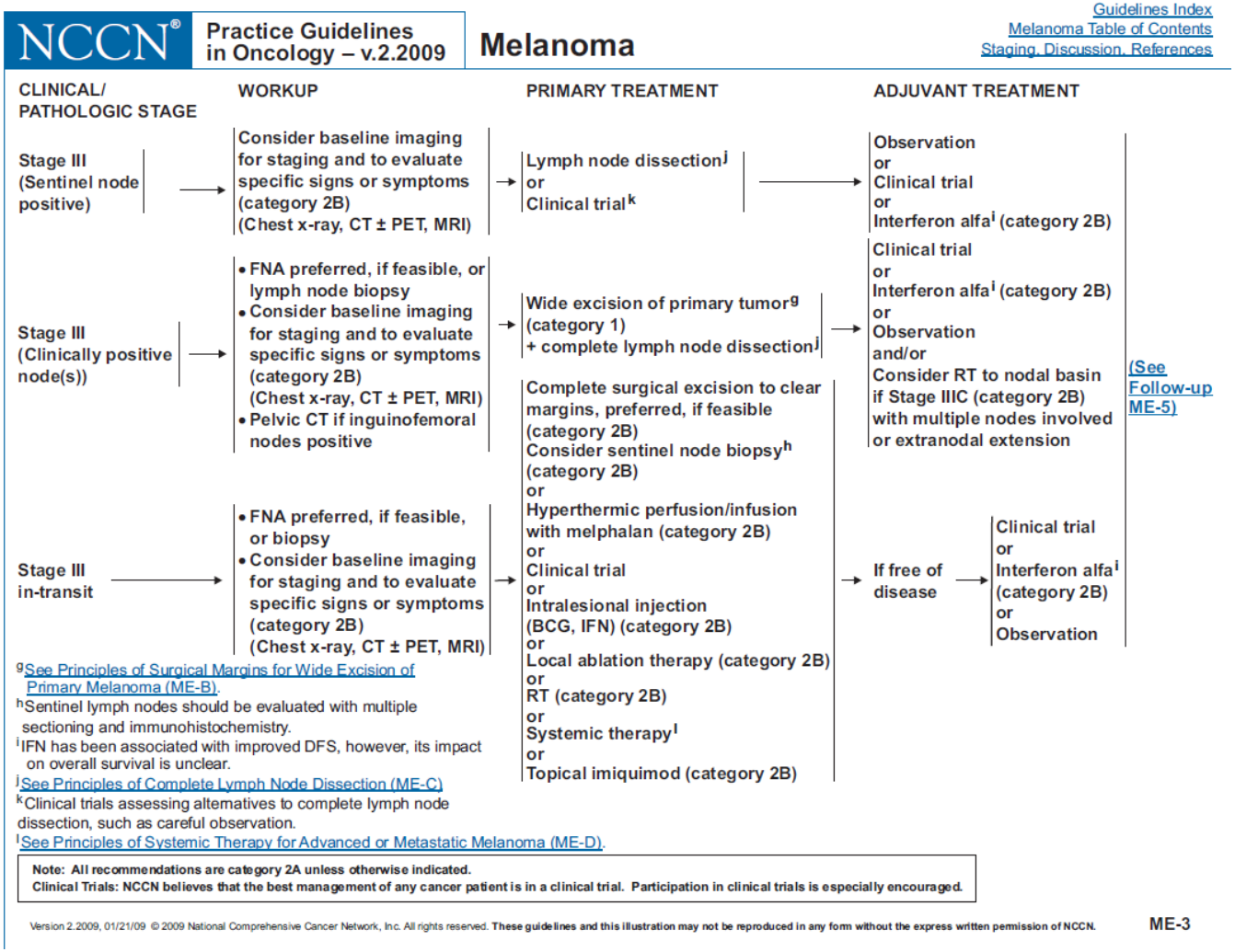
1. A comprehensive CER program should be developed to better identify the most effective health care options.
2. A comprehensive CER program should link data from public and private entities to build upon existing data collection efforts and research capabilities.
3. CER studies should support the development of "personalized" or stratified medicine.
4. Processes should be developed to ensure that information gained through CER is incorporated into clinical practice and better informs decisions made among patients, their health care providers, and payers.

How will the elements and characteristics of a comprehensive CER program facilitate personalized medicine at the clinical frontline?

# The case of Sarah S

- 37 year-old nurse, red haired, Irish
- Tumor characteristics:
  - 3mm ulcerated primary on posterior right arm
  - Single positive sentinel lymph node
  - 0/10 nodes positive on axillary dissection
- Stage IIIB melanoma
  - 47% risk of death at 5 years
  - Standard regimen: 1 month high-dose interferon, 11 months moderate dose; lowers risk of relapse ~10% with unclear impact on survival
  - Associated symptoms: fatigue, mood disturbance, autoimmune dysfunction
- Patient concerns:
  - Family history: Mother died from melanoma
  - Infertility

# Adjuvant interferon for Sarah S?



NCCN® Practice Guidelines in Oncology – v.2.2009

## Melanoma

Guidelines Index
Melanoma Table of Contents
Staging, Discussion, References

| CLINICAL/ PATHOLOGIC STAGE | WORKUP | PRIMARY TREATMENT | ADJUVANT TREATMENT |
|---|---|---|---|
| Stage III (Sentinel node positive) | Consider baseline imaging for staging and to evaluate specific signs or symptoms (category 2B) (Chest x-ray, CT ± PET, MRI) | Lymph node dissection[j] or Clinical trial[k] | Observation or Clinical trial or Interferon alfa[i] (category 2B) |
| Stage III (Clinically positive node(s)) | • FNA preferred, if feasible, or lymph node biopsy • Consider baseline imaging for staging and to evaluate specific signs or symptoms (category 2B) (Chest x-ray, CT ± PET, MRI) • Pelvic CT if inguinofemoral nodes positive | Wide excision of primary tumor[g] (category 1) + complete lymph node dissection[j] | Clinical trial or Interferon alfa[i] (category 2B) or Observation and/or Consider RT to nodal basin if Stage IIIC (category 2B) with multiple nodes involved or extranodal extension |
| Stage III in-transit | • FNA preferred, if feasible, or biopsy • Consider baseline imaging for staging and to evaluate specific signs or symptoms (category 2B) (Chest x-ray, CT ± PET, MRI) | Complete surgical excision to clear margins, preferred, if feasible (category 2B) Consider sentinel node biopsy[h] (category 2B) or Hyperthermic perfusion/infusion with melphalan (category 2B) or Clinical trial or Intralesional injection (BCG, IFN) (category 2B) or Local ablation therapy (category 2B) or RT (category 2B) or Systemic therapy[l] or Topical imiquimod (category 2B) | If free of disease → Clinical trial or Interferon alfa[i] (category 2B) or Observation |

(See Follow-up ME-5)

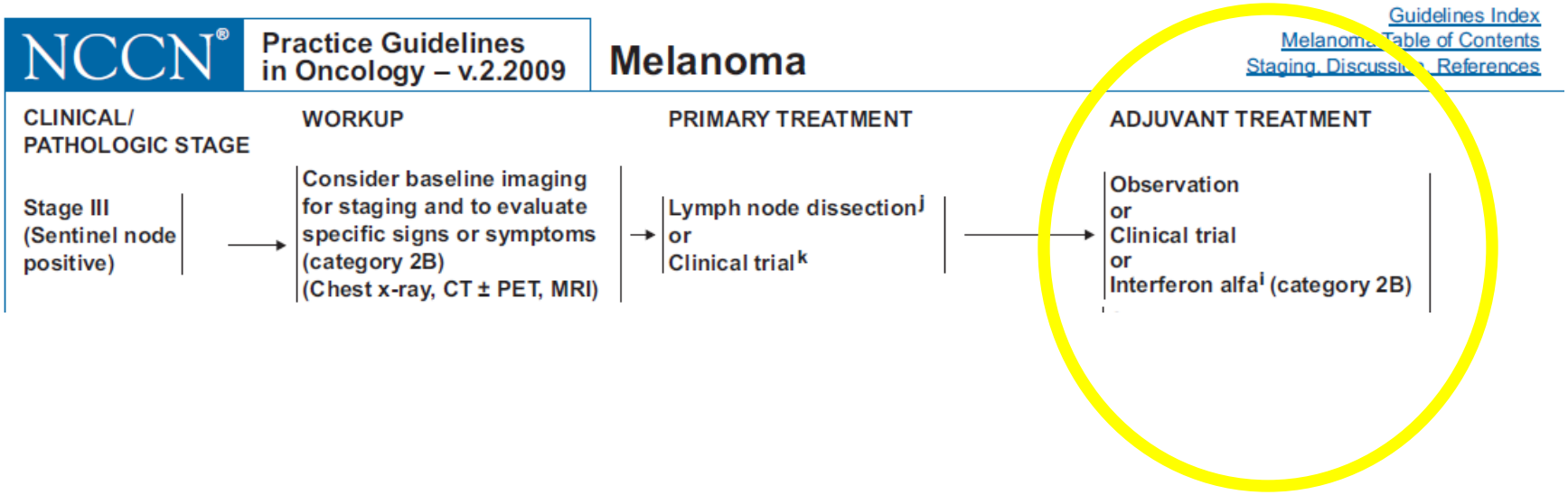
[g] See Principles of Surgical Margins for Wide Excision of Primary Melanoma (ME-B).
[h] Sentinel lymph nodes should be evaluated with multiple sectioning and immunohistochemistry.
[i] IFN has been associated with improved DFS, however, its impact on overall survival is unclear.
[j] See Principles of Complete Lymph Node Dissection (ME-C)
[k] Clinical trials assessing alternatives to complete lymph node dissection, such as careful observation.
[l] See Principles of Systemic Therapy for Advanced or Metastatic Melanoma (ME-D).

**Note: All recommendations are category 2A unless otherwise indicated.**
**Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.**



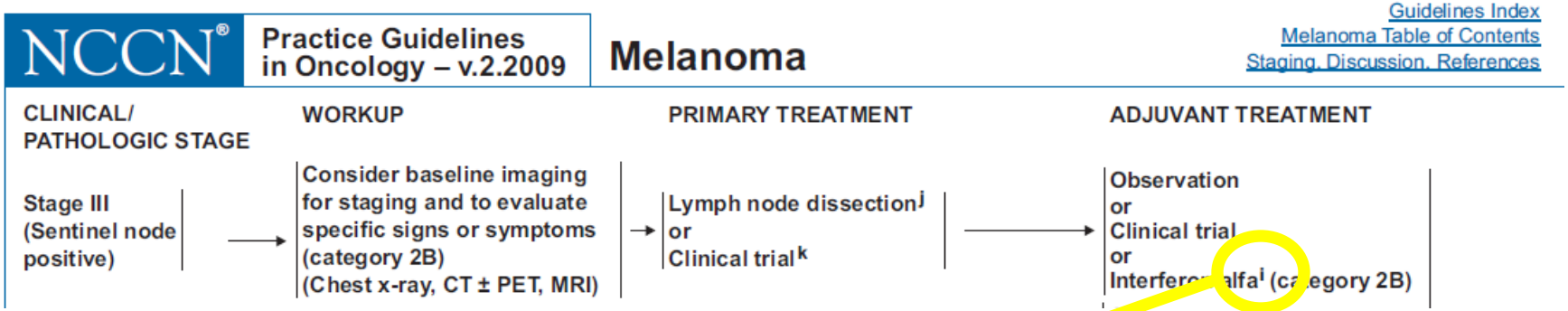
ME-3

# Adjuvant interferon for Sarah S?




**Observation vs Clinical Trial vs Interferon**

# Adjuvant interferon for Sarah S?




**i. IFN has been associated with improved DFS, however, its impact on overall survival is unclear**

# Relapse free and overall survival with high dose adjuvant interferon

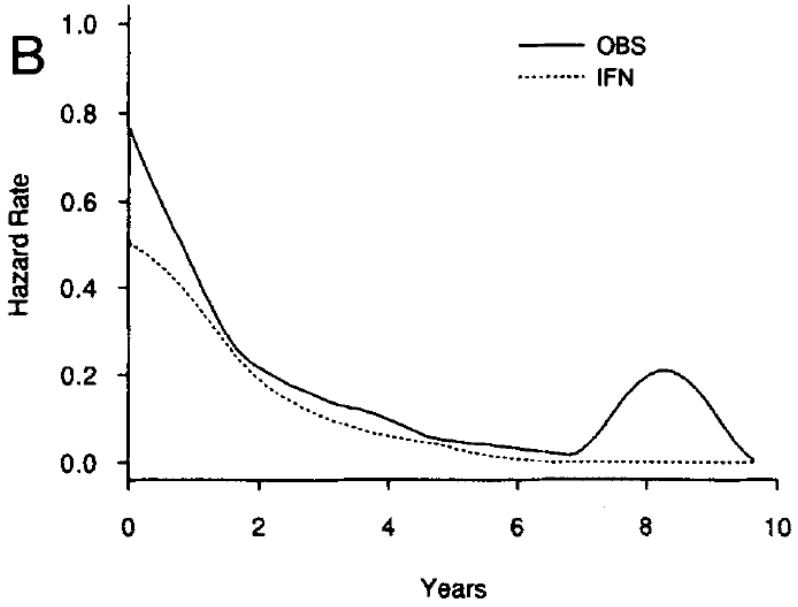



Fig 2. Relapse-free survival of eligible patients (A) and estimated hazard of relapse over time for eligible patients participating in E1684 (B). OBS, observation.

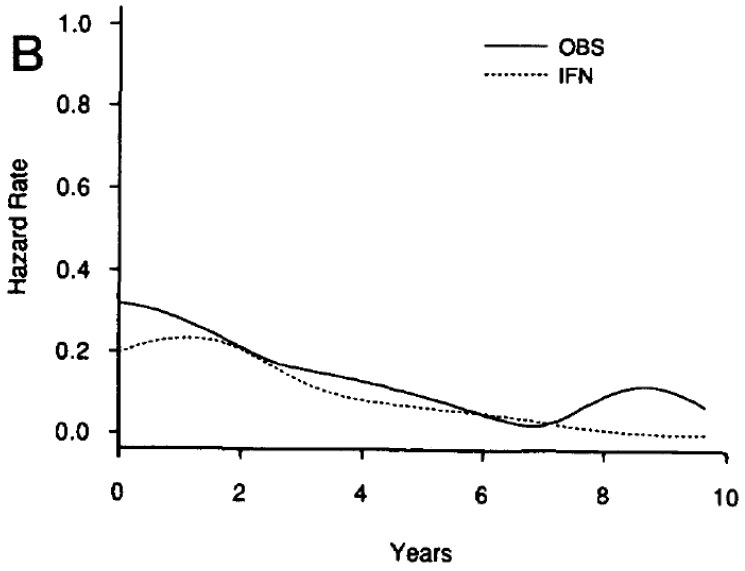



Fig 3. Overall survival of eligible patients (A) and estimated hazard of death over time for eligible patients participating in E1684 (B).

Kirkwood et al, JCO 1996 14: 7-17.

# Impact of interferon on quality of life

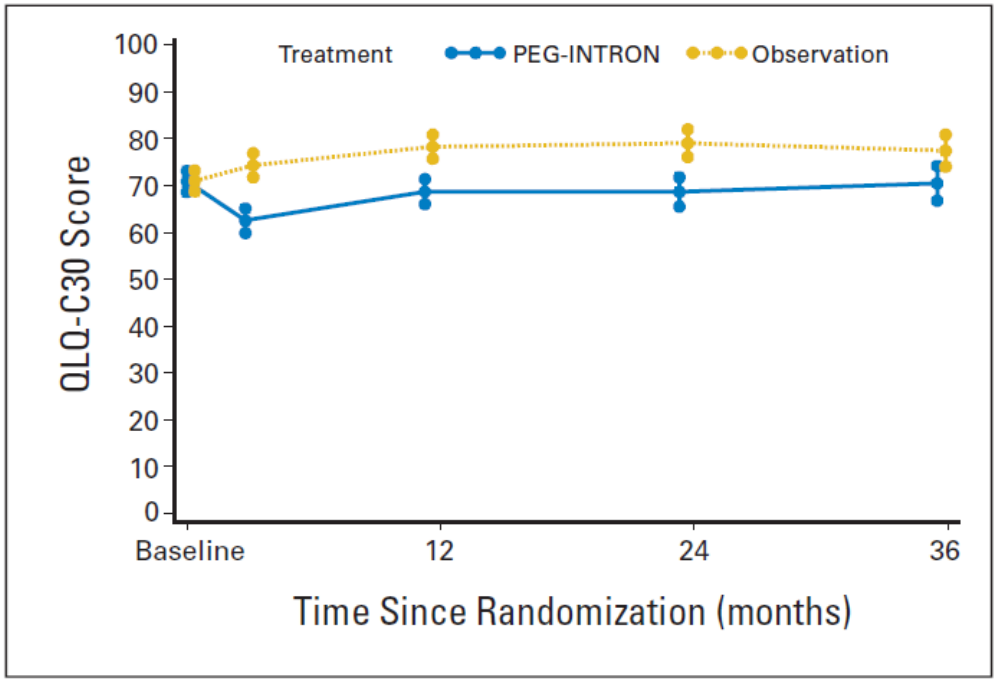



**Fig 3.** Primary health-related quality-of-life end point. Quality of Life Questionnaire (QLQ) -C30 scores for global health status and quality of life, measured by mean score plus 99% CI. PEG-INTRON, pegylated interferon alfa-2b.

Bottomley et al, JCO 2009 27: 2916-23.

# Can we shorten the treatment period?

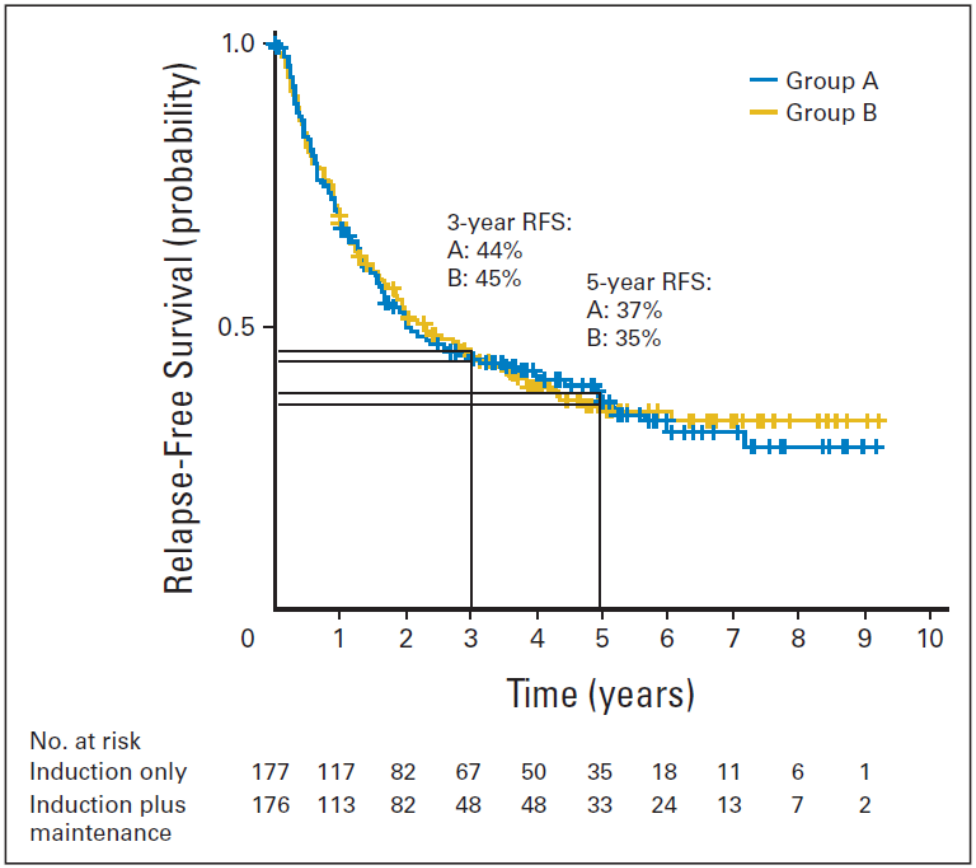


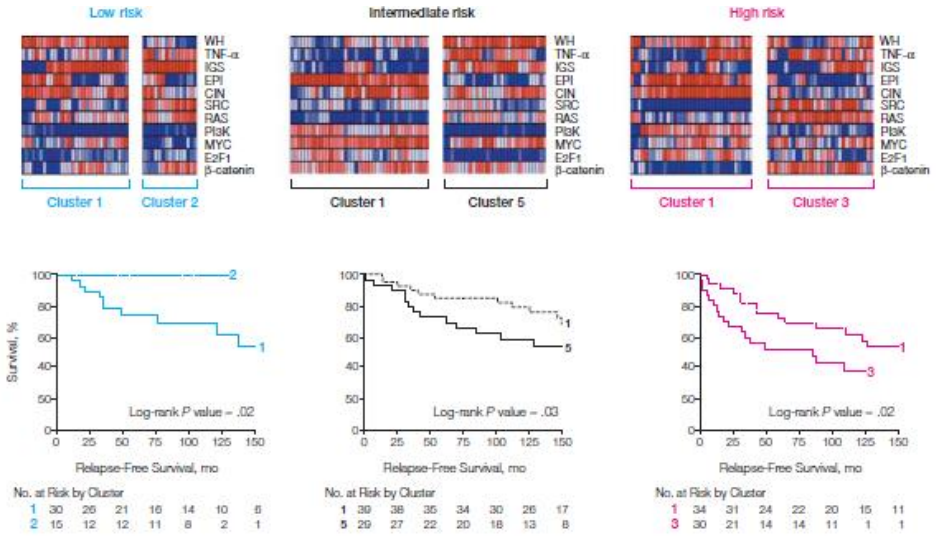

**Fig 2.** Kaplan-Meier curves for relapse-free survival (RFS) in the two randomization groups. Blue line, arm A; gold line, arm B.

Pectasides et al, JCO 2009 27: 939-44.

# Will newer information help?

ABL
AKT1
AKT2
BRAF
CDK
CTNNB1 (b-catenin)
EGFR
ERBB2 (HER2)
FBX4
FBXW7
FGFR1
FGFR2
FGFR3
FLT3
GNAQ
HRAS
KIT
KRAS
MEK1
MET
NRAS
PDGFRA
PIK3CA
PTPN11
RET
SOS1
TP53

Molecular mutation analyses for melanoma provided by Oregon




Gene expression signatures, clinicopathological features, and individualized therapy in breast cancer. Acharya CR, et al
JAMA. 2008 Apr 2;299(13):1574-87.

# The case of Sarah S

- Can generally predict Sarah's risk of death but cannot refine and personalize these estimates using data from recently treated patients or published clinical trials
- Cannot determine the right adjuvant management plan – for Sarah
- Cannot tell Sarah the risk of infertility after treatment
- Cannot guide Sarah on the direct impact on her personal quality of life, nor the influence of worries about her mother's death
- Sarah's clinical case will not contribute to the care of people in the future unless she is enrolled in a specific clinical trial

# Friends of Cancer Report Recommendations

1. A comprehensive CER program should be developed to better identify the most effective health care options.
2. A comprehensive CER program should link data from public and private entities to build upon existing data collection efforts and research capabilities.
3. **CER studies should support the development of "personalized" or stratified medicine.**
4. Processes should be developed to ensure that information gained through CER is incorporated into clinical practice and better informs decisions made among patients, their health care providers, and payers.

# Expanded body of evidence

- CER trials using broad inclusion criteria to simulate “real-world” populations
- Large population-based studies
  - Registries (e.g., SEER)
  - Large clinical datasets (e.g., Medicare)
  - Large research datasets (e.g., caBIG)
- Diverse study designs to maximize usable information

➢ Wealth of information, potentially applicable to the individual patient, now available to the clinician.

# Interoperable datasets

- Up-to-date information on the latest scientific research
- Public/private coordination
- Linking of data from clinical research networks and health care databases
- Leveraging of existing initiatives and resources (e.g., caBIG, BIG Health, Medicare, VA, Kaiser)

➢ Hypotheses generated about reasons for differing responses between groups of patients (e.g., by race, ethnicity, age, sex), which then could be used to design appropriate clinical trials.

# Data availability

- Data security and protection of PHI
- Researcher access
  - Enable clinical scientists to pose questions that will enable more specific tailoring of care
- Clinician access
  - Requires front-end dashboard to support use
  - Must increase productivity, efficiency, and quality of care

➢ A feasible mechanism for clinicians to use the available data, to personalize care for the individual patient.

# Data use

- Examination of racial, ethnic, geographic, and socioeconomic variations in care and outcomes
- Study of all health care options for a given condition
- Evaluation of clinical outcomes across a variety of settings and patient populations
- Feedback to clinicians on the outcomes of their choices
- Evaluation of information generated through CER studies in conjunction with current clinical practice guidelines
- Rational and scientific basis for reimbursement decisions

➢ A system that provides useful information to providers, patients, policy-makers, and payers.

# CER and personalization of medical care

- Emphasis placed not only on the “average” patient, but also on the minority who experience prolonged survival or improved quality of life

- Examine “success factors” across datasets to identify factors that may optimize the current patient’s outcomes.
- Use biomarkers or other clinical characteristics to identify the individual’s unique susceptibilities and likely response to treatment(s).

# CER and personalization of care (cont.)

- Analyses of data from an integrated data network

- Identify factors that contribute to disease susceptibilities and differences in clinical outcomes, to enable informed decision-making for the individual patient.
- Exploit large volume of data to understand what happened for prior patients with similar characteristics to the current individual patient.

# CER and personalization of care (cont.)

- Prospective clinical studies (including randomized trials) to further explore real-world effectiveness, characterize subpopulations for which a therapy is effective, and collect biospecimens to measure predictive markers.

- Make high-quality data available to the clinician, to select the most likely-to-succeed option for the individual patient.
- Enable prediction of individual response to treatment.

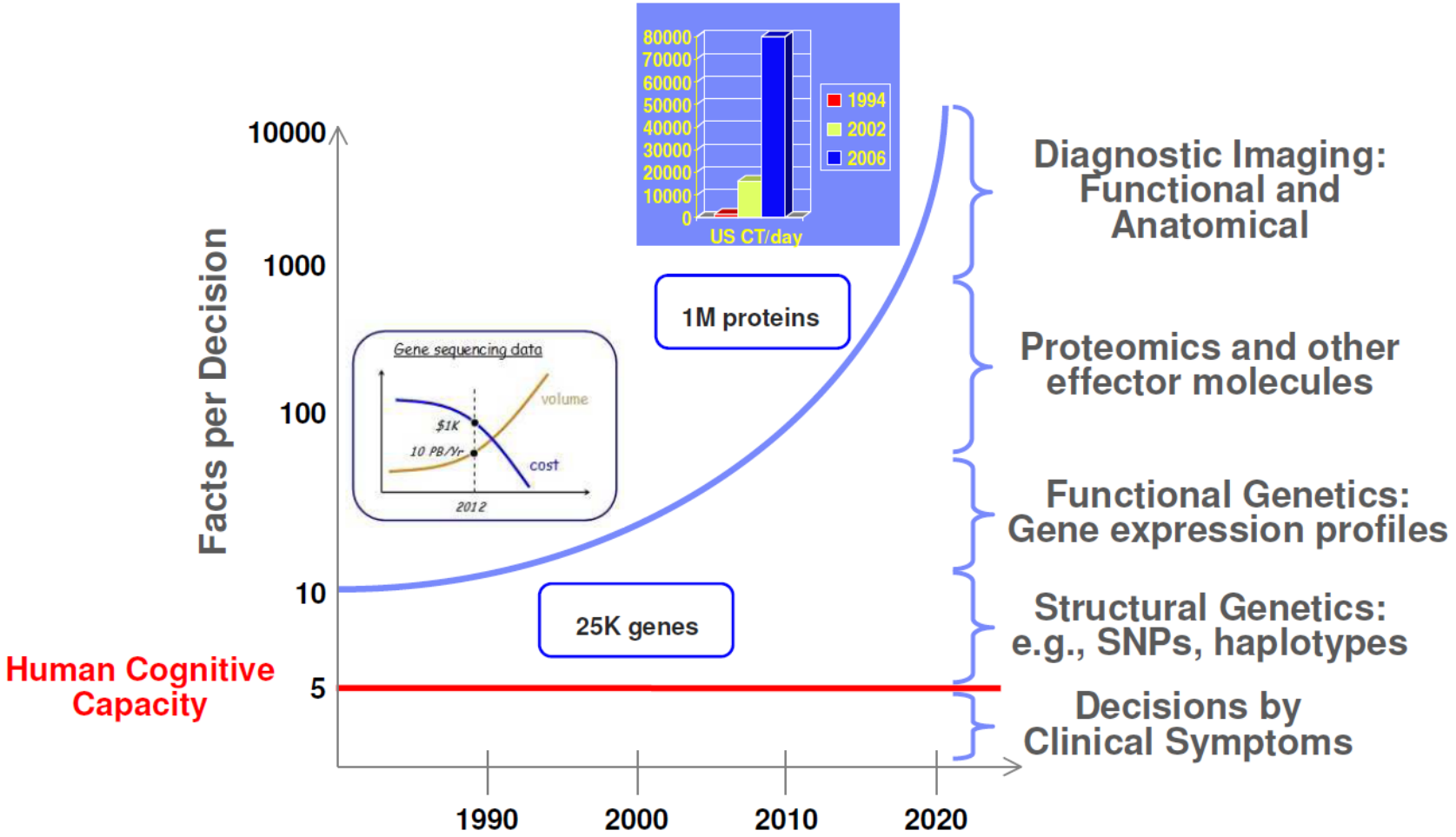
# CER and personalization of care (cont.)

- Utilization of all types of research methods and of more efficient research techniques.

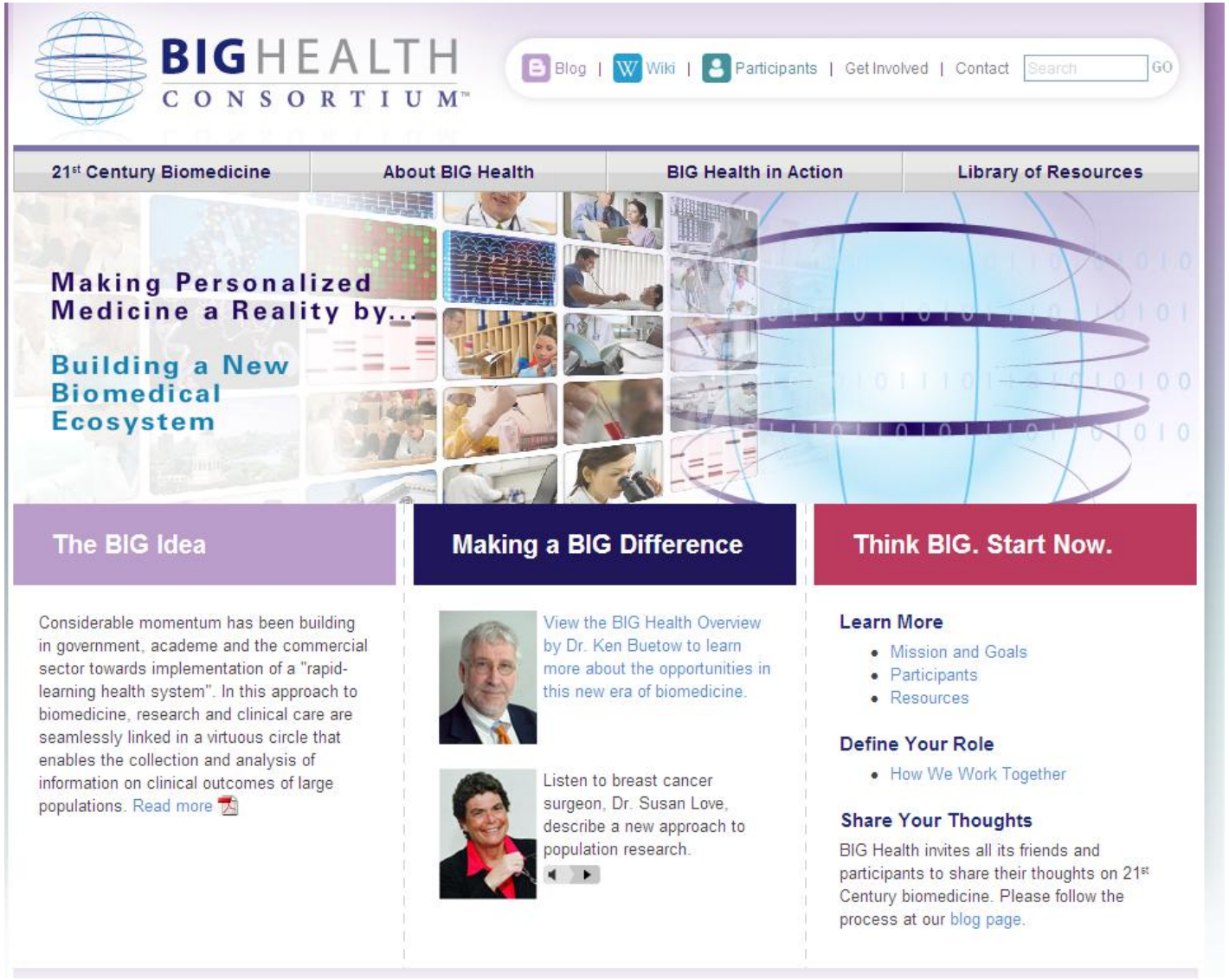
- Answer questions relevant to the individual patient's care and outcomes through flexible use of diverse study designs and analytic methods.

# Oh no!

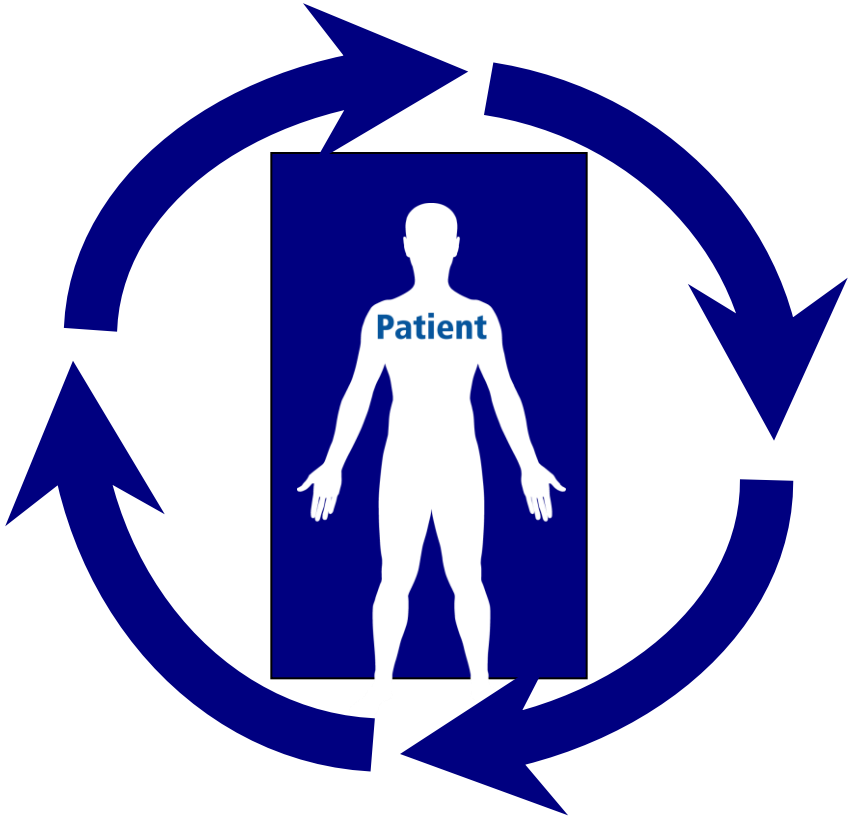
## Challenges are Data Explosion and Cognitive Overload



# Realizing this vision together



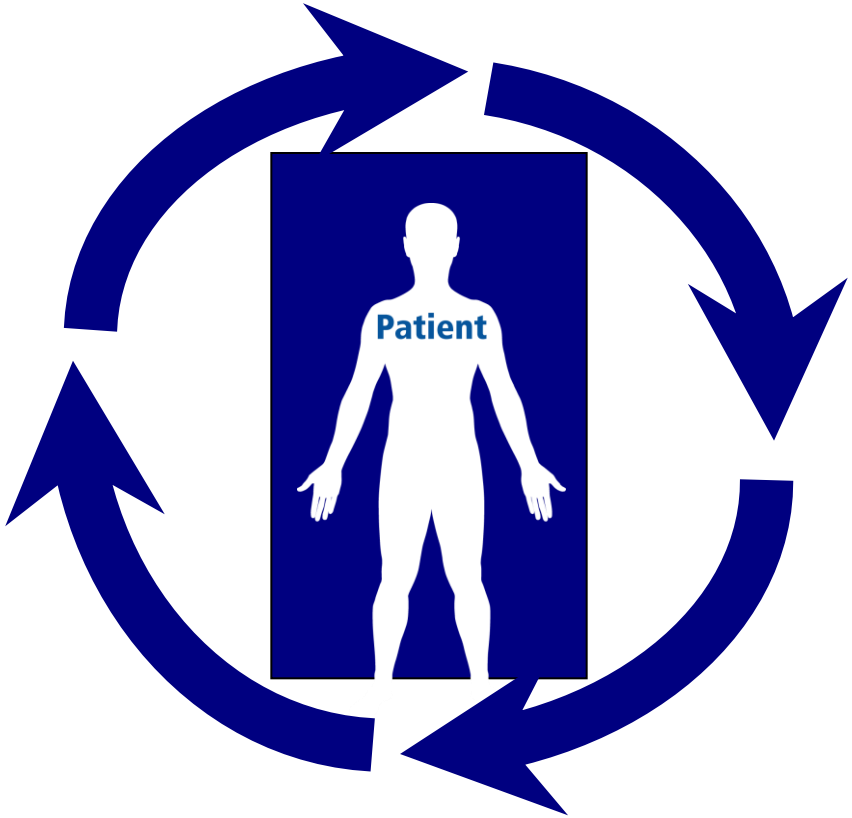
# Rapid Learning Healthcare – IOM 2007




Data that are routinely collected in patient care feed into an ever-growing databank, or set of coordinated databases.

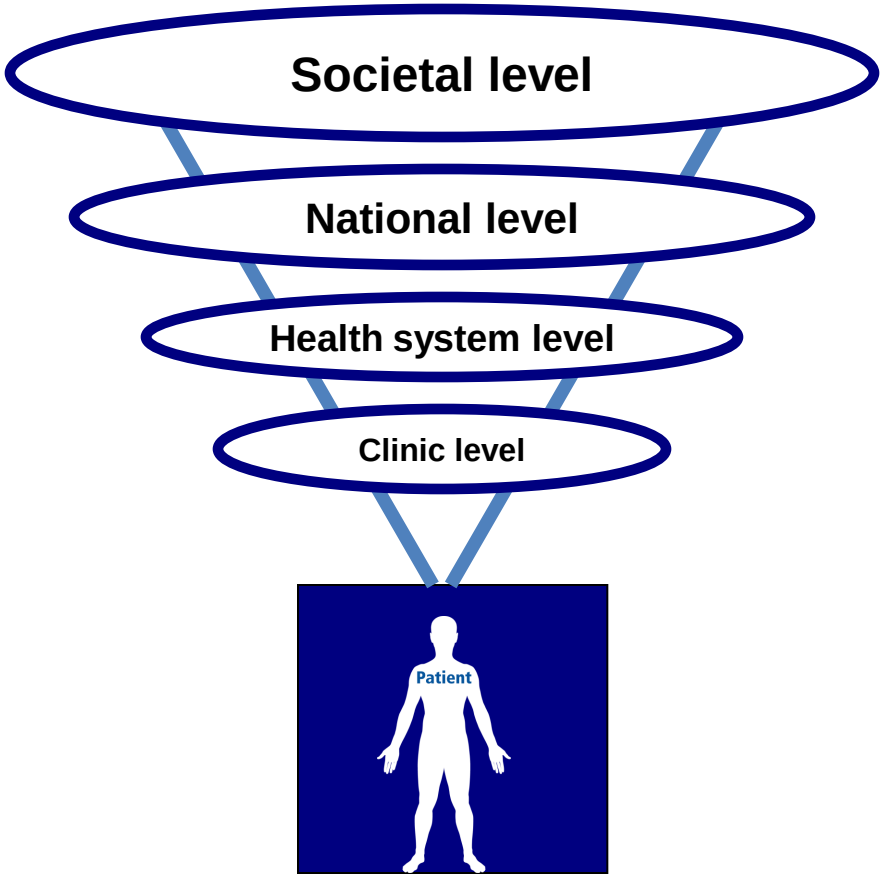
The system learns by routinely analyzing captured information, iteratively generating evidence, and constantly implementing new insights into subsequent care.

# Rapid Learning Healthcare: A path to CER & PM




- generate and apply the best evidence relevant to each patient
- propel scientific discovery “as a natural outgrowth of patient care;” and,
- support quality assessment and improvement, spark innovation, enhance patient safety, and allow payers to maximize healthcare value

# Perspective is fundamental – especially for CER & PM



# Personalized CER and Sarah

- Tumor characteristics, past medical history, family history, genomics & biomarkers, imaging, patient reported outcomes, and personal values shape care
- 5 months interferon (1 month high-dose, 4 months moderate-dose) optimizes survival.
- With a <6-month regimen, risk of infertility in a 37yo woman at 5 years is 20%.
- If she gets pregnant, risk of secondary melanoma primaries is 40%.

→ **Data can be used to inform discussion, support clinical decisions, promote new discovery and tailor her care while managing her symptoms/experiences.**

# Personalized CER now?

- Where are we in terms of personalized CER in current oncology practice?
- Where are we going?
- What does this mean for providers and patients?

# The case of Belinda M

- 55 y.o. woman
- Mother of two grown children, homemaker, and volunteer with Meals on Wheels
- 1.3 cm hormone receptor positive breast cancer
  - Lumpectomy and axillary dissection
  - Intermediate grade tumor
  - Node negative
  - Hormone receptor positive
  - Her2/*neu* negative
  - Genomic test to predict tumor-specific risk

- Adjuvant chemotherapy?

# Tumor specific prediction is possible

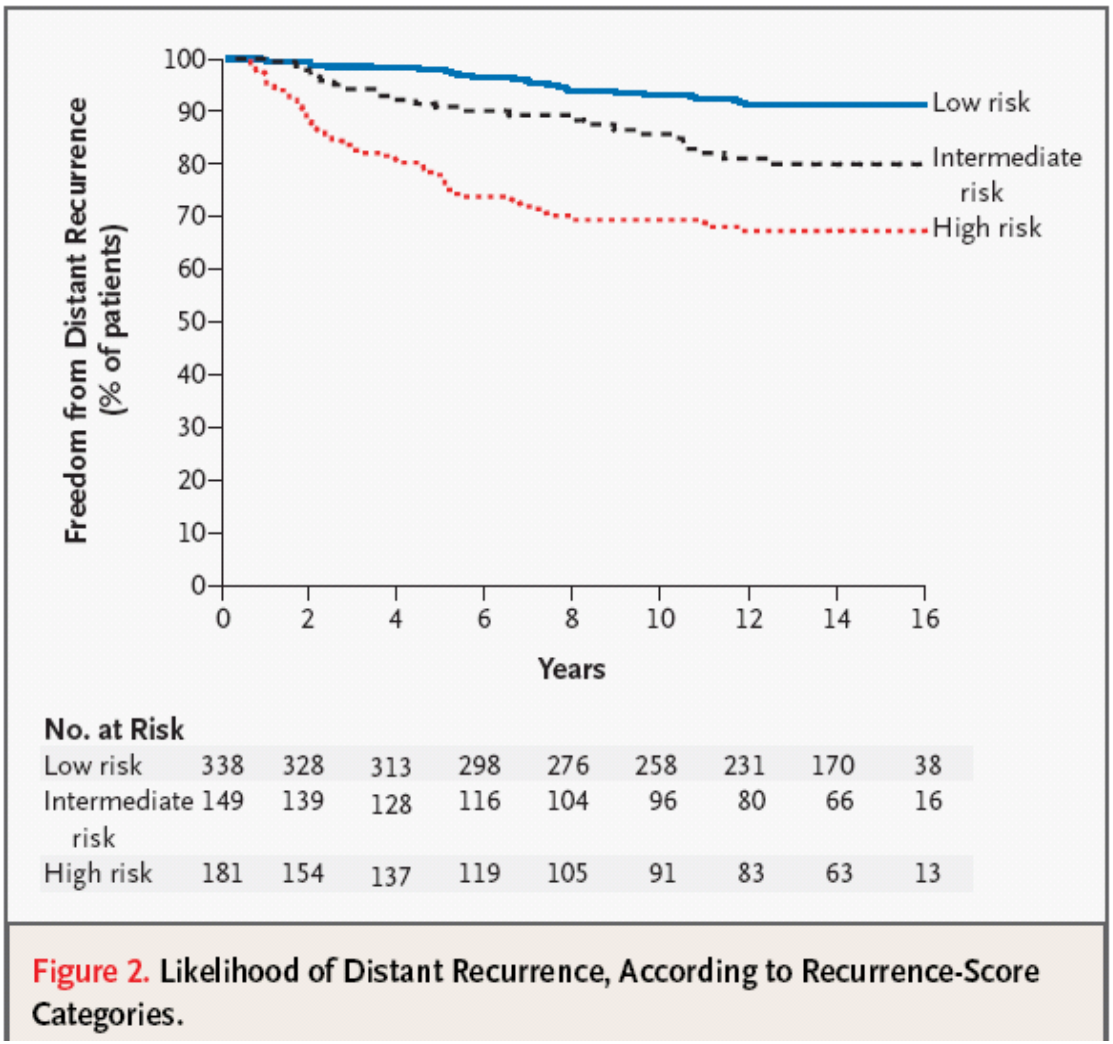
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## A Multigene Assay to Predict Recurrence of Tamoxifen-Treated, Node-Negative Breast Cancer

Soonmyung Paik, M.D., Steven Shak, M.D., Gong Tang, Ph.D., Chungyeul Kim, M.D., Joffre Baker, Ph.D., Maureen Cronin, Ph.D., Frederick L. Baehner, M.D., Michael G. Walker, Ph.D., Drew Watson, Ph.D., Taesung Park, Ph.D., William Hiller, H.T., Edwin R. Fisher, M.D., D. Lawrence Wickerham, M.D., John Bryant, Ph.D., and Norman Wolmark, M.D.

N Engl J Med 351;27-30, 2004




**No. at Risk**

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Low risk | 338 | 328 | 313 | 298 | 276 | 258 | 231 | 170 | 38 |
| Intermediate risk | 149 | 139 | 128 | 116 | 104 | 96 | 80 | 66 | 16 |
| High risk | 181 | 154 | 137 | 119 | 105 | 91 | 83 | 63 | 13 |

**Figure 2. Likelihood of Distant Recurrence, According to Recurrence-Score Categories.**

Risk score predicts likelihood of recurrence without chemotherapy.

N Engl J Med 351;27-30, 2004

# Tailoring of treatment

Belinda has her tumor tested and has a recurrence score of 10.

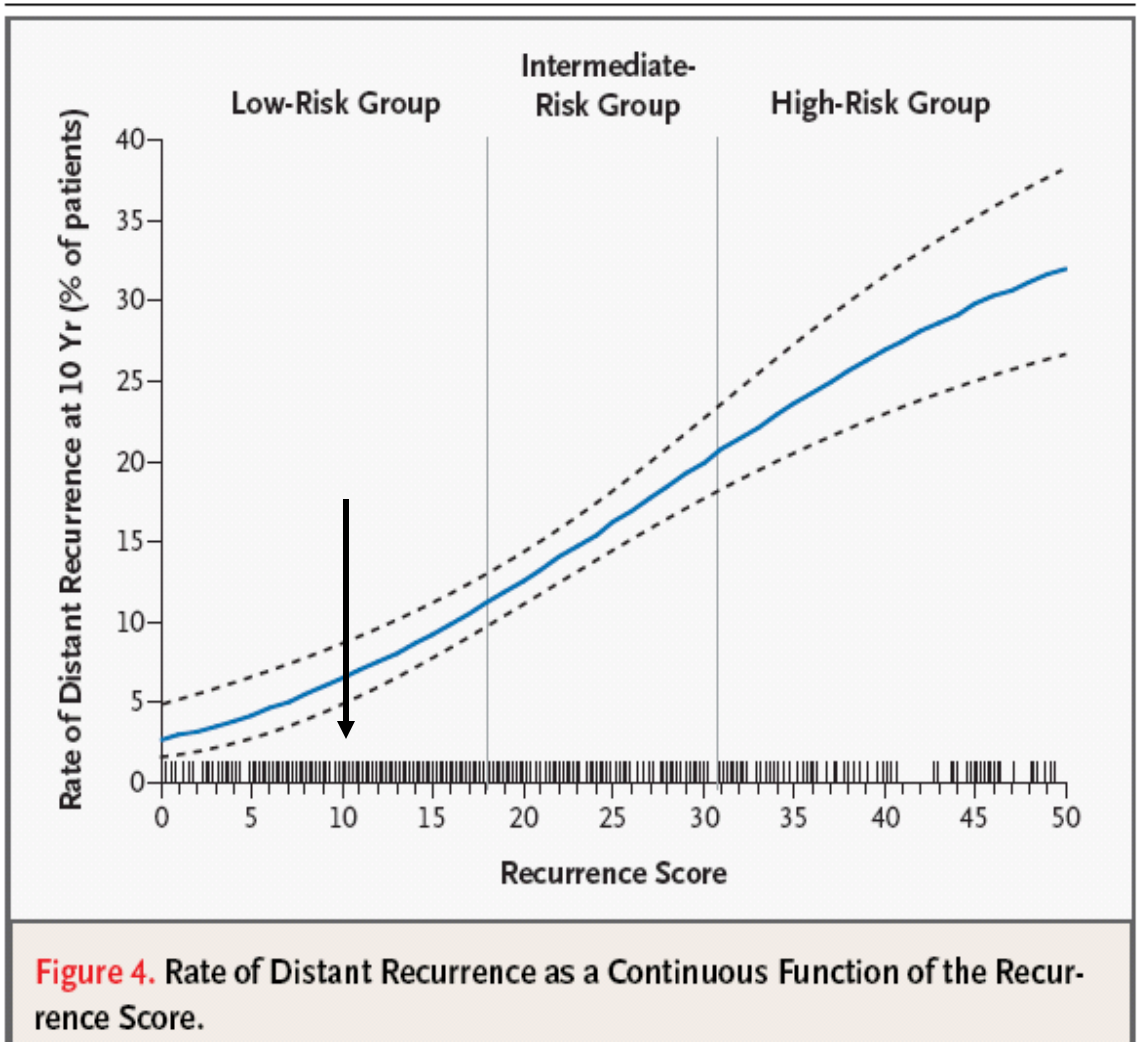
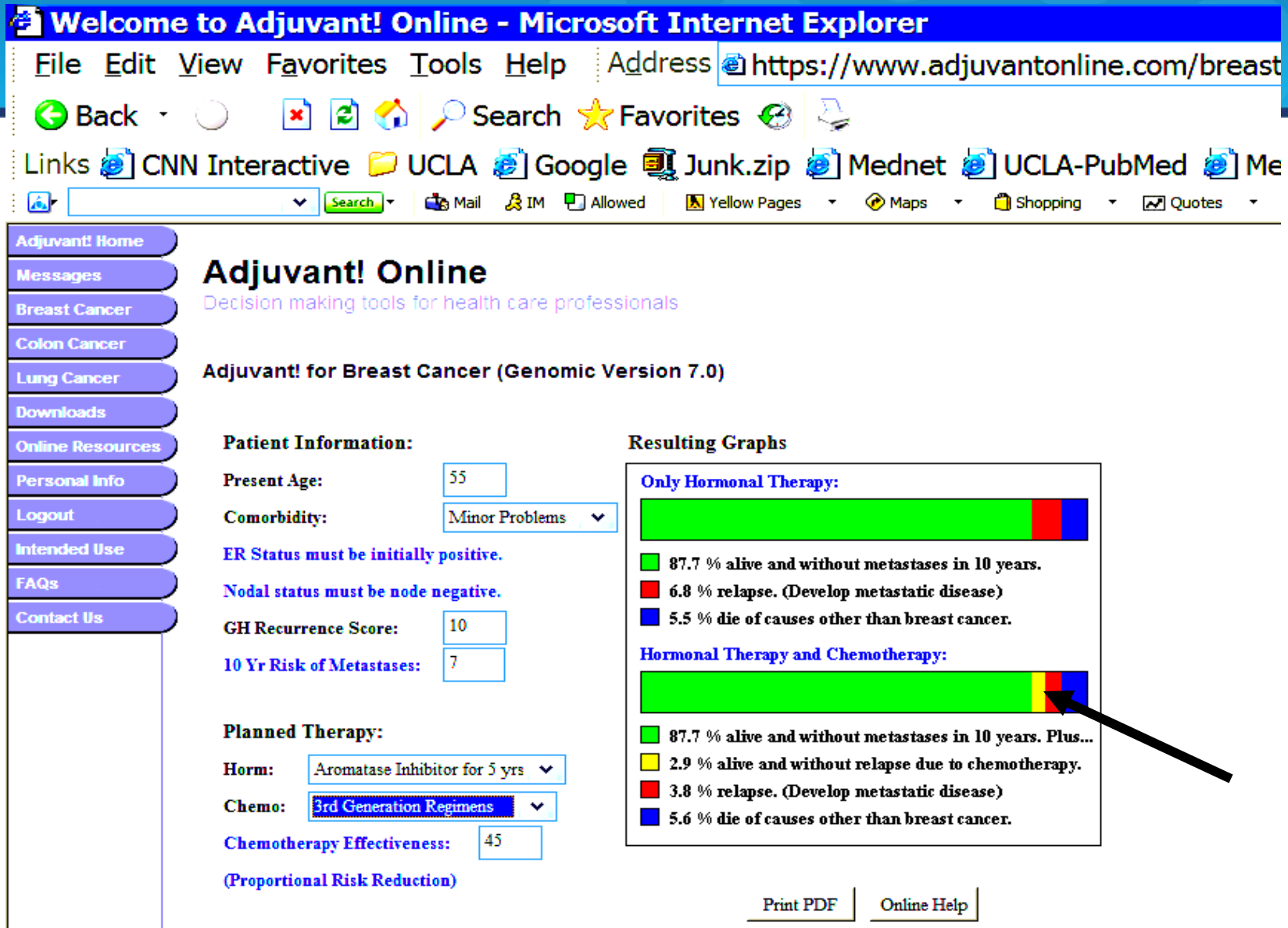



Figure 4. Rate of Distant Recurrence as a Continuous Function of the Recurrence Score.




Chemotherapy adds only 2.9% absolute benefit

# Personalized CER – where are we going?

- Integration of data generated in research and clinical settings to the care of this individual patient
- Myriad data sources – clinical, administrative, patient reported, genomic, clinical trials, imaging, pathology
- Suites of decision-support tools, with tailored output specific for the individual patient
- Interaction with both patients and providers, including greater democracy of information
- Information provided at point of care or wherever the user needs it most