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?
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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**

<table>
<thead>
<tr>
<th>CLINICAL/PATHOLOGIC STAGE</th>
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<th>ADJUVANT TREATMENT</th>
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<tr>
<td>Stage III (Sentinel node positive)</td>
<td>Consider baseline imaging for staging and to evaluate specific signs or symptoms (category 2B) (Chest x-ray, CT ± PET, MRI)</td>
<td>Lymph node dissection[^1] or Clinical trial[^k]</td>
<td>Observation or Clinical trial or Interferon alfa[^l] (category 2B)</td>
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| 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 inguinal/femoral nodes positive | Wide excision of primary tumor[^3] (category 1) + complete lymph node dissection[^l] | Complete surgical excision to clear margins, preferred, if feasible (category 2B)  
Consider sentinel node biopsy[^h] (category 2B)  
Hyperthermic perfusion/infusion with melphalan (category 2B)  
Clinical trial  
Intralesional injection (BCG, IFN) (category 2B)  
Local ablation therapy (category 2B)  
RT (category 2B)  
Systemic therapy[^1] or  
Topical imiquimod (category 2B)  
(See Follow-up ME-5) |
| 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) | | If free of disease  
Clinical trial or Interferon alfa[^l] (category 2B) or Observation |

[^1]: See Principles of Surgical Margins for Wide Excision of Primary Melanoma (ME-B).
[^3]: Sentinel lymph nodes should be evaluated with multiple sectioning and immunohistochemistry.
[^k]: IFN has been associated with improved DFS, however, its impact on overall survival is unclear.
[^3]: See Principles of Complete Lymph Node Dissection (ME-C).
[^h]: Clinical trials assessing alternatives to complete lymph node dissection, such as careful observation.
[^1]: 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.

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**Guidelines Index**

Melanoma Table of Contents  
Staging, Discussion, References

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**PMC Personalized Medicine Coalition**

**National Pharmaceutical Council**

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Adjuvant interferon for Sarah S?

Observation vs Clinical Trial vs Interferon
### Adjuvant interferon for Sarah S?

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\(^i\) FN 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).

Impact of interferon on quality of life

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

Can we shorten the treatment period?

![Graph showing Kaplan-Meier curves for relapse-free survival (RFS) in the two randomization groups. Blue line, arm A; gold line, arm B.]

**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?

Molecular mutation analyses for melanoma provided by Oregon

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.
1. A comprehensive CER program should be developed to better identify the most effective health care options.

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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.
• 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.
Challenges are Data Explosion and Cognitive Overload

- Diagnostic Imaging: Functional and Anatomical
- Proteomics and other effector molecules
- Functional Genetics: Gene expression profiles
- Structural Genetics: e.g., SNPs, haplotypes
- Decisions by Clinical Symptoms

Human Cognitive Capacity

Facts per Decision

1M proteins

25K genes

1990 2000 2010 2020
Realizing this vision together

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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

- Societal level
- National level
- Health system level
- Clinic level

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?
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.

Risk score predicts likelihood of recurrence without chemotherapy.
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