Coverage with Evidence Development

False Hope: Bone Marrow Transplantation for Breast Cancer
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Multiple Methodologies

- Literature searches & analyses; document analyses; both comprehensive & focused
- Review of media coverage (Nexus-Lexis)
- Interviews-snowball ID; semi-structured; repeats; face-to-face, telephone, & site visits
- Legal analysis: (1) all reported cases 1988-2002 (4 jury trials, 88 litigated) & leading cases; (2) interviews of defense & plaintiffs’ lawyers
- Utilization data: HCUP, Registry; Response
- Clinical trials: systematic review methods
The HDC/ABMT Experience

Clinical utilization path (off protocol) ~23,000–40,000

- Court trials: 1991-99
  (for-profit; not-for-profit cancer centers
- Mandates: 1994 ff, OPM, states

Clinical evaluation path (on protocol) ~1,000

- Technology assessments: 1988-96
  (OHTA, BSC, BCBSA, AMA, Aetna, ECRI, Kaiser, ICSI)
- Randomized clinical trials: 1990-2003
  (E/PBT-01, CALGB 9082, INT-0121, SWOG 9623)
  (European and international trials)
- ASCO: 1999
- Audits: 2000
The Fateful Branching: Two Pathways, Two “Systems”

- The “Rational System” of Evaluation
  - Emphasizes systematic evaluation of evidence by technology assessments, clinical practice guidelines, & randomized clinical trials

- The “Default System” of Clinical Use
  - Reflects uncoordinated action driven by Phase 2 studies, patients, physicians, lawyers, media, entrepreneurs, state & federal governments
The Face of the Patient

- Pamela Pirozzi 1989; Arlene Betzner 1990; Angela Davis 1988-92; Ricki Dienst; Anne Grant; Virginia Hetrick
- Est. 23,000-40,000 women received HDC/ABMT for breast cancer; ~600 premature deaths; ~1,000 on protocol
- Median age, 1993-2000, 44-47 years
- Median length of stay, 24 - 19 days
- Median charges, $103,924 - $71,760; est. total cost over 10 years, $2 billion
- Payers: PPO/FFS, 53.9%; HMO, 23.4%
Number of Women with Breast Cancer and High Dose Chemotherapy 1993-2001

- Number of women with HDC
- Number of women with breast cancer and HDC
- Percent of HDC for breast cancer
The Basic Issues

- Access to new treatments:
  - Claims of individuals vs. those of society?

- Evaluation: What is essential?
  - Phase 2 studies vs. Phase 3 RCTs
    - RCTs generally required for Breast CA treatments

- Role of health insurers:
  - Require evidence or pay for experimental therapy (conflicts with exp/invest exclusion)?
What is a Medical Procedure?

- No adequate lexicon exists to describe medical interventions comprehensively.
- Narrowly defined, a procedure is what a physician does to a patient as specified in *Current Procedural Terminology, Standard Edition*.
- Broadly defined, a procedure is any medical intervention that is not a therapeutic product, especially not a drug.
Emergence of a Procedure

- Elements of HDC/ABMT for breast cancer:
  - Combination chemotherapy
  - Adjuvant chemotherapy
  - High-dose chemotherapy
  - Bone marrow transplantation
  - Growth factors
- Phase 2 studies (single-site, small numbers)
- Transplanters and a defining procedure
The HDC/AMBT Procedure

- Administering standard chemotherapy to determine tumor responsiveness, then . . .
- Harvesting bone marrow and/or stem cells
- Administering HDC (2X-10X standard dose)
- Reinfusing bone marrow and/or stem cells
- Adding growth factor
- Providing supportive care & monitoring for substantial toxicity of the procedure
Evaluation: Drugs vs. Procedures

- **New Drugs**
  - Required by FDA; prescribed in law, regulation & other guidance documents
  - Financed by sponsors

- **New Procedures**
  - Negotiated between medical profession & insurers
  - Financing uncertain
    - NIH/NCI
    - Insurers: any role?
      - Standard coverage?
      - CED?
Drivers of Clinical Use: The Default System

- Phase 2 studies & physician legitimation
- Patient demand & physician advice
- Litigation
- The print & broadcast media
- Entrepreneurial oncology & the “market”
- State & federal government mandates
Legitimation of Use & Evaluation

• Medicine (esp. oncology) has high legitimacy:
  – FDA should facilitate access to new cancer drugs
  – Phase 2 studies generate “promise”
  – Standard of care is elastic
  – Promising therapy becomes best chance for a cure
    • Concept of “best available therapy”
  – “Dream Team” document argues effectiveness
  – Physician advocacy is unconstrained by science

• Health insurers have very low or no legitimacy:
  – Unevaluated treatments not covered or reimbursed
  – Clinical research not the business of insurers
  – Coverage denials invite challenges
Litigation Trends
(“Maddeningly Unpredictable”)

- Fox v. HealthNet, 1993: $89 M verdict
- Litigation peaks in 1993-94
- No pre- or post-Fox outcome differences
  - 1988-1993: insurers, 17; patients, 16
  - 1994-2002: insurers, 26; patients, 28
  - Four jury verdicts are mixed
- Settlements strongly favor patients after Fox
Primary Legal Issues

• Contract interpretation:
  – exp/invest exclusion; medical necessity clause; chemotherapy coverage; BMT coverage; specific HDC/ABMT exclusion
• Standard of care
• Informed consent
• Bad faith denial of claims
• Expert witnesses & clinical trial evidence
• Sympathy & emotion
Attorneys’ Perspectives

• Defense attorneys
  – Cases never winnable: sympathetic patients; arrogant administrators
  – Relied on testimony of medical directors:
    • HDC experimental
    • Few experts
    • Physician opponents unwilling to testify
  – Reasonable exclusions, not bad faith
  – Appropriate venue: clinical trials

• Plaintiffs' attorneys
  – Contractual ambiguity used to undermine exclusion
  – Community oncology demonstrated wide use
  – Relied on Peters & Antman to counter experimental
  – Insurers acted in bad faith by inconsistency
  – Appropriate venue: court trials
Entrepreneurial Oncology

• Oncology non-existent as a subspecialty in 1971
  – Rapid growth of community oncologists

• Response Technologies/Response Oncology
  – IMPACT Centers: between academic centers and oncologist’s office (an intermediate site of care)
  – Protocols: registered trials with FDA; but no RCTs
  – Centralized data collection; publications

• Not-for-profit academic oncology deemed inaccessible for many patients “needing” ABMT
Response Technologies/Oncology: Number of Centers

Cumulative Number of RT-RO Centers
Number of RT-RO Centers per year
OPM Mandates Coverage of HDC/ABMT for Breast Cancer

- U.S. House of Representatives: August 1994 hearing
  - Women’s health issue emphasized
  - “Coin-flip” trials derided
  - OPM reliance on NCI severed
- Office of Personnel Management FEHBP
  - HDC/ABMT coverage denied beforehand
  - “Change of heart” experienced afterwards
State Mandated Coverage of HDC/ABMT for Breast Cancer (1996)

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The “Rational” Evaluation System

• Technology assessments – Insurers, others
• Randomized clinical trials - NCI
• Clinical practice guidelines - NCCN
• Systematic reviews of evidence - Cochrane
• Audits of randomized trials
  – U.S.: Cancer cooperative groups
  – International
Technology Assessments

- NCHSR/OHTA: 1988
  - David Eddy, J Clinical Oncology, 1992
  - Bezwoda 1995; HDC “not worse than” standard chemo
- Aetna: MCOP & independent medical review
- ECRI: 1993; 1994-95; patient brochure
- Others: BSC; TAG; ICSI
- **BUT** 1990 “Dream Team” document argued for coverage (Peters, Lippman, Bonadonna, DeVita, Holland, and Rosner)
Health Insurers & HDC/ABMT Clinical Trials

• HDC/ABMT advocates (researchers & physicians):
  – Insurers should finance clinical trials
  – Insurers should finance “standard of care” treatment

• Insurers respond (predictively & creatively):
  – Coverage of HDC/ABMT typically denied
  – US HealthCare: financed the “Philadelphia trial”
  – BCBSA: established the Demonstration Project
  – Aetna: launched independent medical review (MCOP)
BCBSA TEC Clinical Trial Demonstration Project

- Standard coverage
  - Part of reimbursement
  - Paid for by plans
  - Post-pay for procedure
  - Existing contracts, often w/ BMT centers
  - Paid from premiums
  - Existing plan-based offices & staff

- Demonstration project
  - Not in reimbursement
  - Paid by BCBSA
  - Pre-paid for procedure
  - New contracts
  - Paid from other sources
  - Dedicated central office & staff
  - Based on “equipoise”
NCI High-Priority Clinical Trials

- SWOG 9623 (1996, 2005)
US Clinical Trials Accrual
Interactions between Systems

• Clinical use enhanced perversely by evaluation:
  – Initiation of Phase 3 RCTs *validates* Phase 2 “promise”
  – Phase 2 authorizes physician discretion & enthusiasm

• Evaluation suffers from widespread clinical use:
  – Recruitment of patients is harder when there is easy access (and coverage) for off-protocol treatment
  – Norms of science do not govern “cross-over” activity, e.g., “expert” testimony, or policy advocacy

• But successful evaluation *may* affect clinical use
ASCO Meeting, May 1999

• Run up to ASCO Meeting:
  – NCI Director’s meeting, 2/99: How do we announce the results of trials?
  – Trial news posted on NCI & ASCO websites in April

• ASCO Meeting:
  – ECOG/PBT-01: Stadtmauer: metastatic, no benefit
  – CALGB: Peters; DSMB; high-risk, no benefit
  – Sweden: J Bergh: no benefit
  – S Africa (Bezwoda 2): benefit
  – France (PEGASE): poster session, no benefit
South African Trial Audits

- US cancer trials require audits
- Bezwoda 2 (ASCO 1999)
  - Can we (U.S. researchers) replicate these results?
  - Let’s do an audit: complex front-end discussions
  - Audit finds fraud; retractions – ASCO, Lancet
- Bezwoda 1 (1995)
  - Only trial reporting benefit; published in *JCO*
  - Influential in reinforcing clinical use
  - U of Witwatersrand invites Weiss back
  - Fraud uncovered once again
Conclusion 1: Initial Conditions (1988-92) Dominate the Story

- Phase 2 studies proliferate & report “promise”
- Media reports highlight patient stories
- Litigation begins
- Insurers deny coverage
- “Standard of care” legitimated
- Entrepreneurs recognize the “market”
- Phase 3 RCTs initiated & proceed slowly
- Intervene at Phase 2 => Phase 3 transition
Conclusion 2: Conflicting Values Are All-pervasive:

- Early access vs. adequate evaluation
- Individual benefit (potential) now vs. collective benefit later
- Experimental procedure vs. standard of care
- Policy discussions emphasize improving “rational system,” not disabling the “default system”
- Protect integrity of evaluation process & provide safety valve for individual cases
Conclusion 3: Institutional Deficit Exists for Evaluating Procedures

• No FDA-equivalent requires evaluation of procedures
  – FDA assets: statute, regulations, administrative agency, history, culture, venue for addressing issues
• Financing evaluation of procedures is problematic
• Public-private partnership recommended
Public-private Partnership

• **Purpose:** evaluate *procedures* by RCTs
• **Partners:** NCI (or NIH), researchers, insurers, patients
• **Actions:**
  – Describe Phase 2 promise & articulate Phase 3 rationale
  – Limit access to new procedures to randomized trials
  – Provide for review of individual cases
• **Benefits:**
  – Parties acknowledge mutual dependence on & common interest in clinical effectiveness
  – Researchers obtain insurer financing of RCTs
  – Provide insurers some litigation protection
  – Public obtains timely data on clinical effectiveness
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Emergence


- Comb therapy
- Hi-dose chemothx
- Bone marrow tx
- Adjuvant therapy
- Growth factors
- Phase 2 studies
- Transplanters

The media tells the story

Patient advocacy
Publications


• Jacobson PD & Doebler SA. “We were all sold a bill of goods”: Litigating the science of breast cancer treatment. *The Wayne Law Review* 2006;52:43-112.