Coverage with Evidence Development

False Hope: Bone Marrow Transplantation for Breast Cancer

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Health Industry Forum

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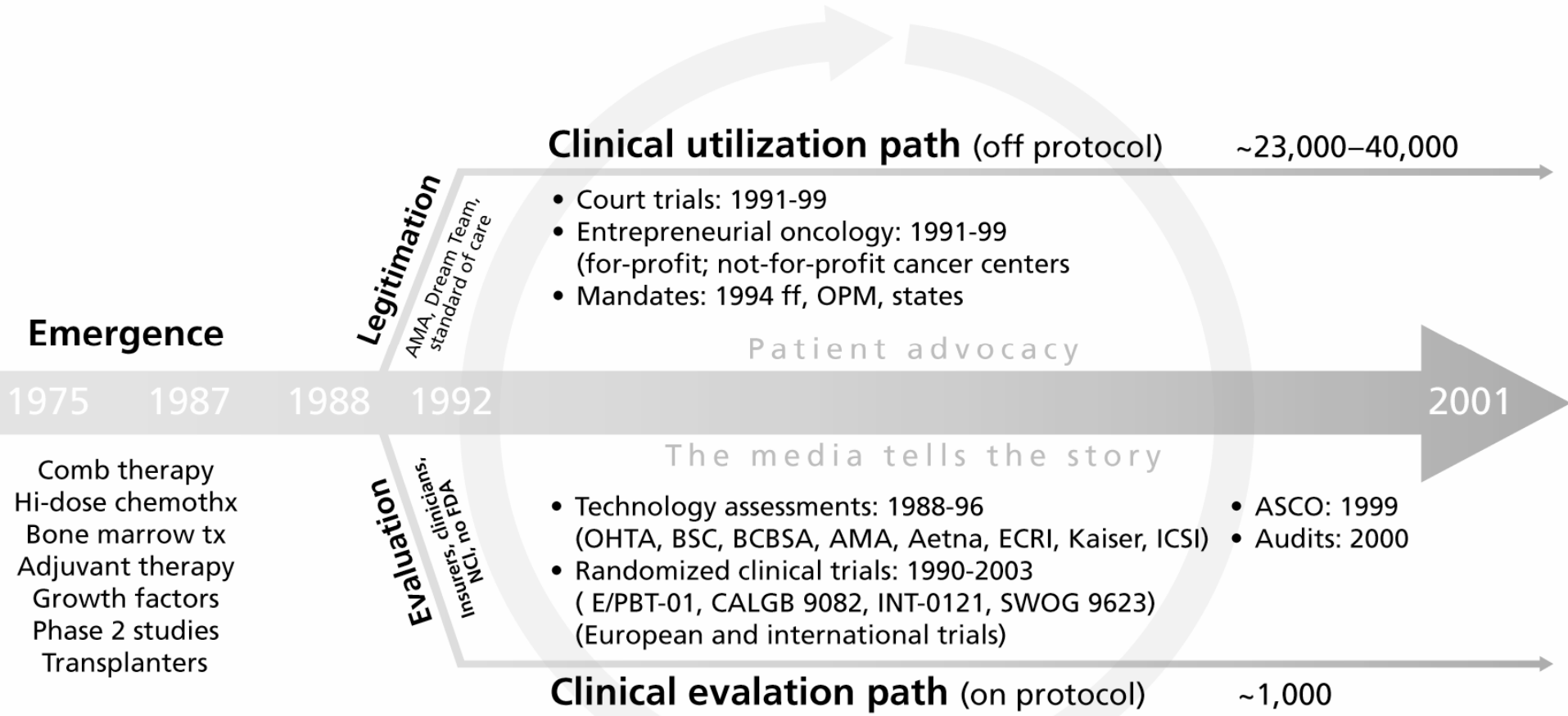
Multiple Methodologies

- 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



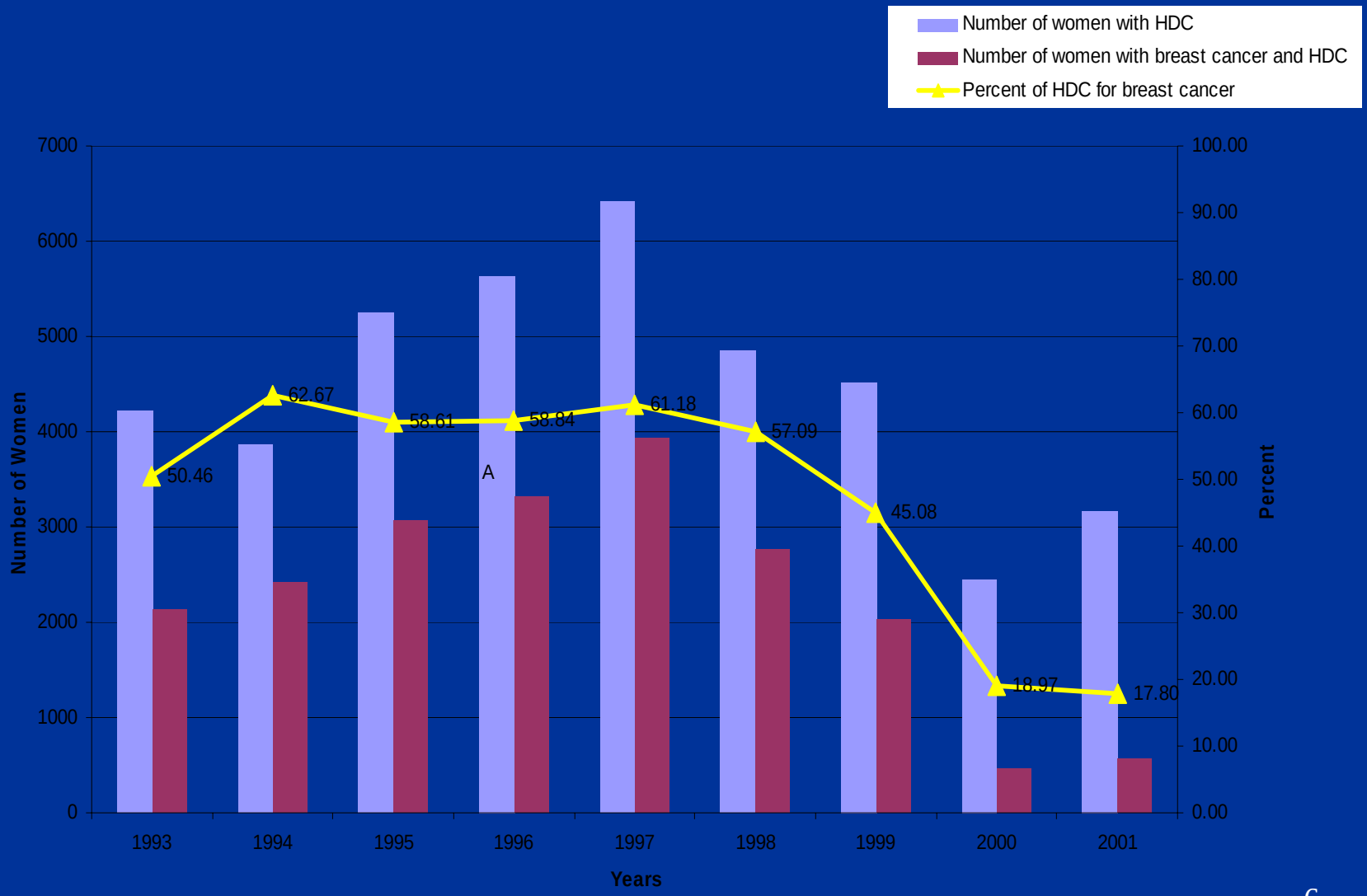
The Fateful Branching: Two Pathways, Two "Systems"

- 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



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

- Administing 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

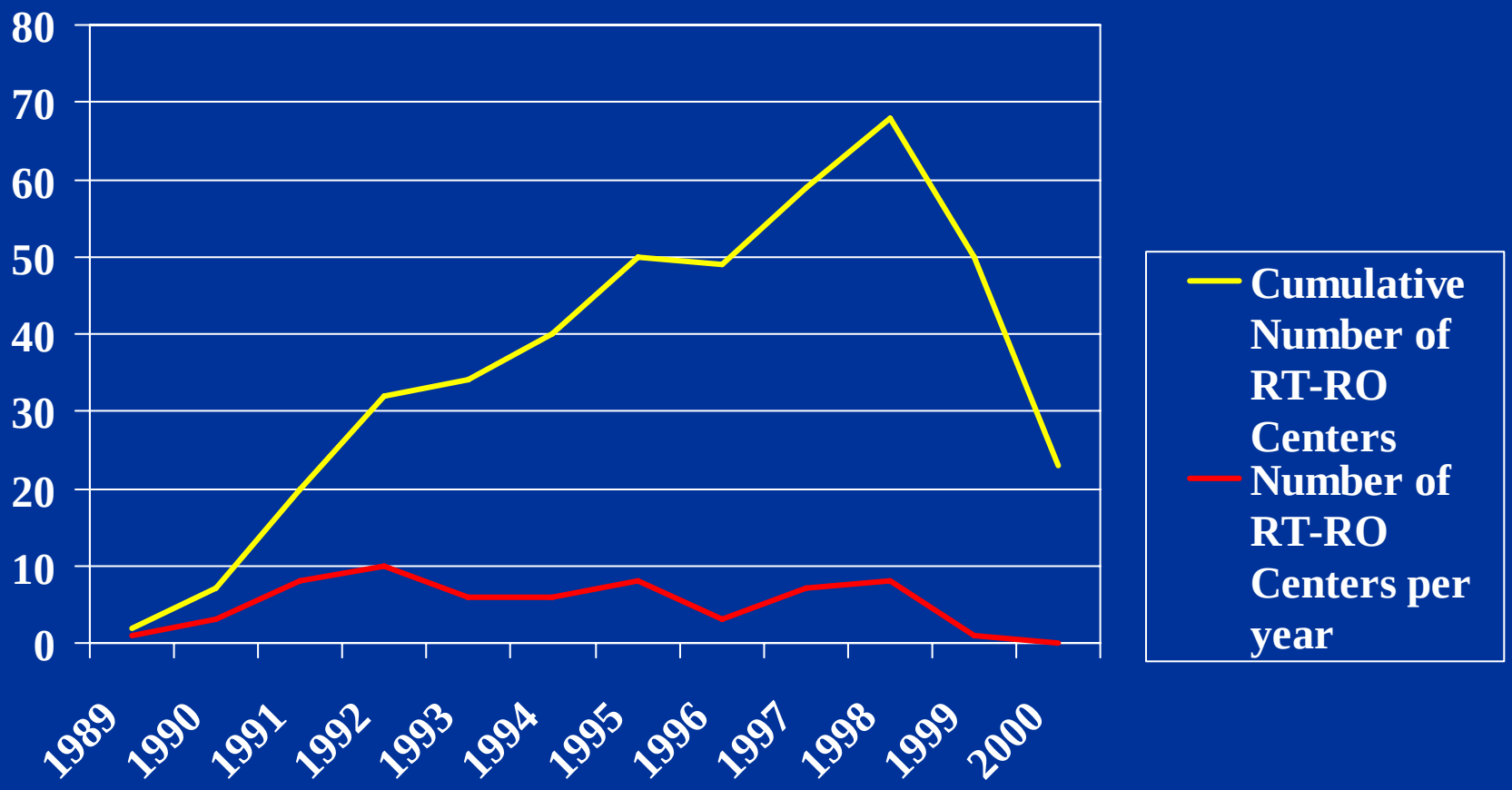
Attorneys' Perspectives

- 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



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)

Massachusetts

Minnesota

Florida

Georgia

Kentucky

California

Louisiana

Tennessee

Missouri

New Hampshire

New Jersey

Virginia

Ohio

New York

Rhode Island

Connecticut

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
- BCBSA: 1988, 1990, 1996
  - 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)

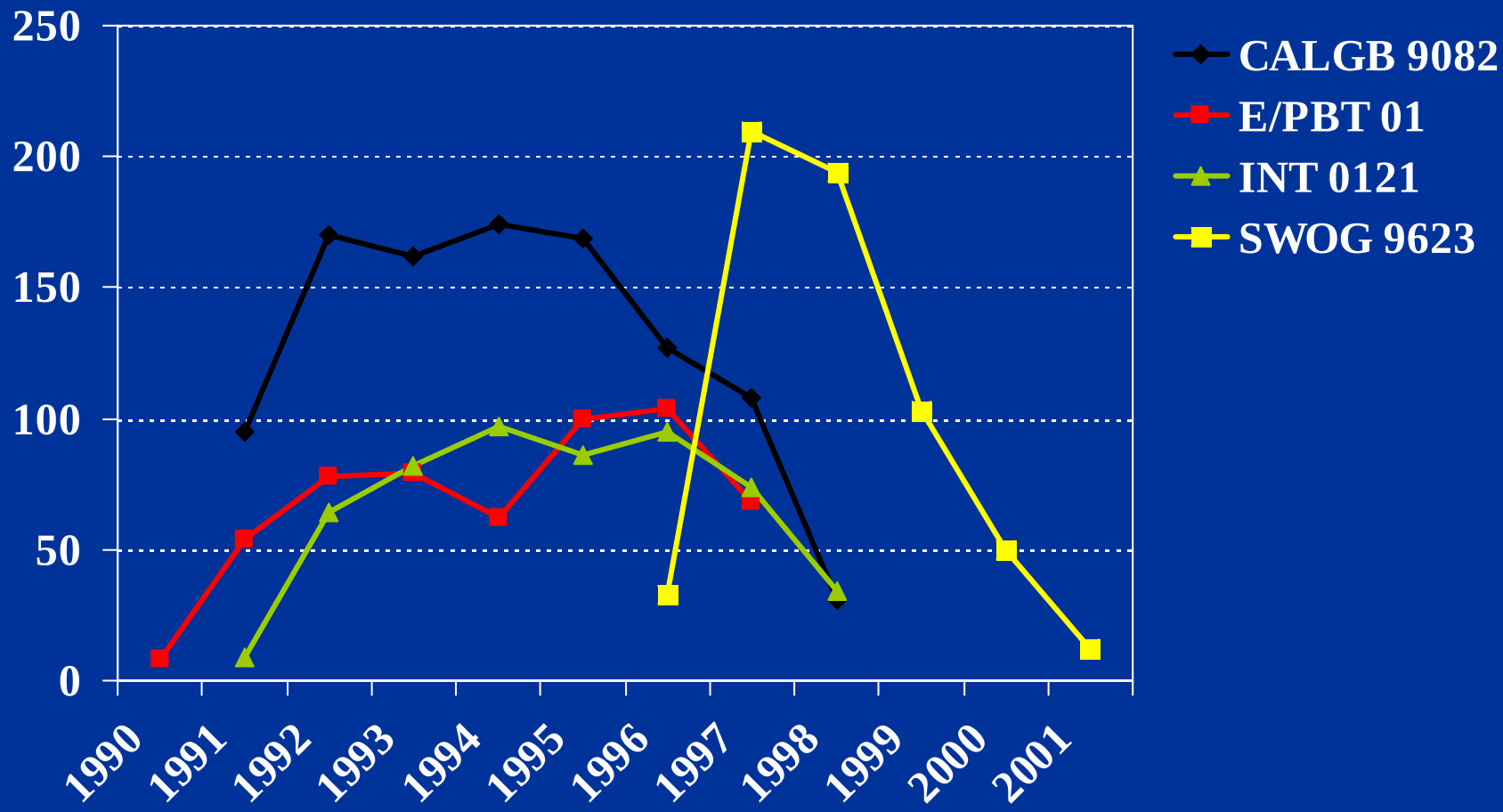
BCBSA TEC Clinical Trial Demonstration Project

- 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

- CALGB 9082/ INT-0163 (1991;1999, 2005)
- PBT-01 => E/PBT-01 (1990-91; 1999, 2000)
- ECOG 2190/INT-0121 (1991-2, 2003)
- 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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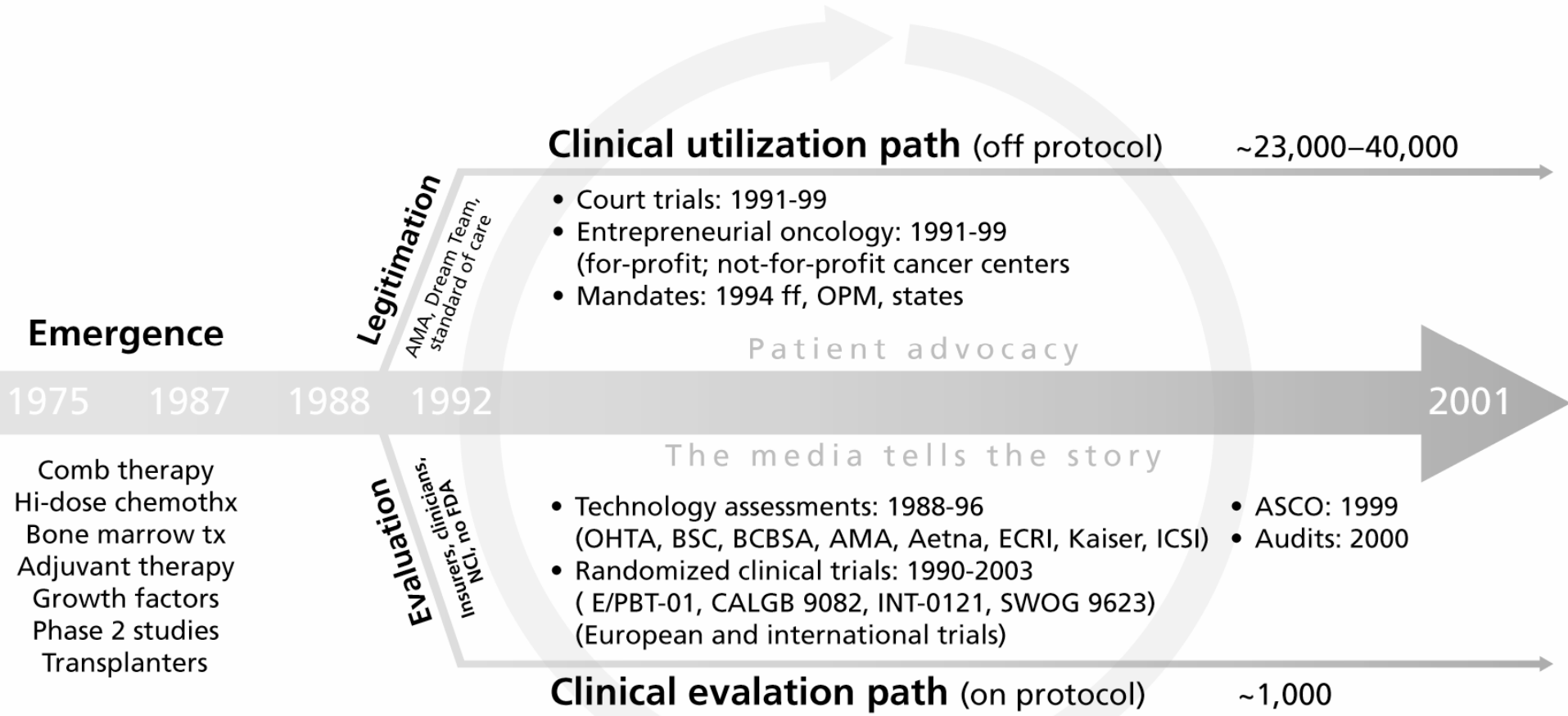

Publications

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