Barrett's Esophagus Translational Research Network (BETRNet) Renewal Concept

Division of Cancer Biology

Division of Cancer Prevention

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Barrett's Esophagus Translational Research Network (BETRNet)

- DCB/DCP multi-disciplinary and multi-institutional program
- Collaboration among multiple centers, with basic and clinical researchers and resource sharing, to tackle a rare cancer
- Significant oversight and active participation by NCI staff allows real-time modifications to the program based on scientific needs and accomplishments
- Enable a deeper understanding of EA biology and its putative precursor lesion, Barrett's esophagus (BE), provide strategies for EA prevention, and better define individuals at risk
- Funded by NCI in 2011; 3 Research Centers and 1 Coordinating Center

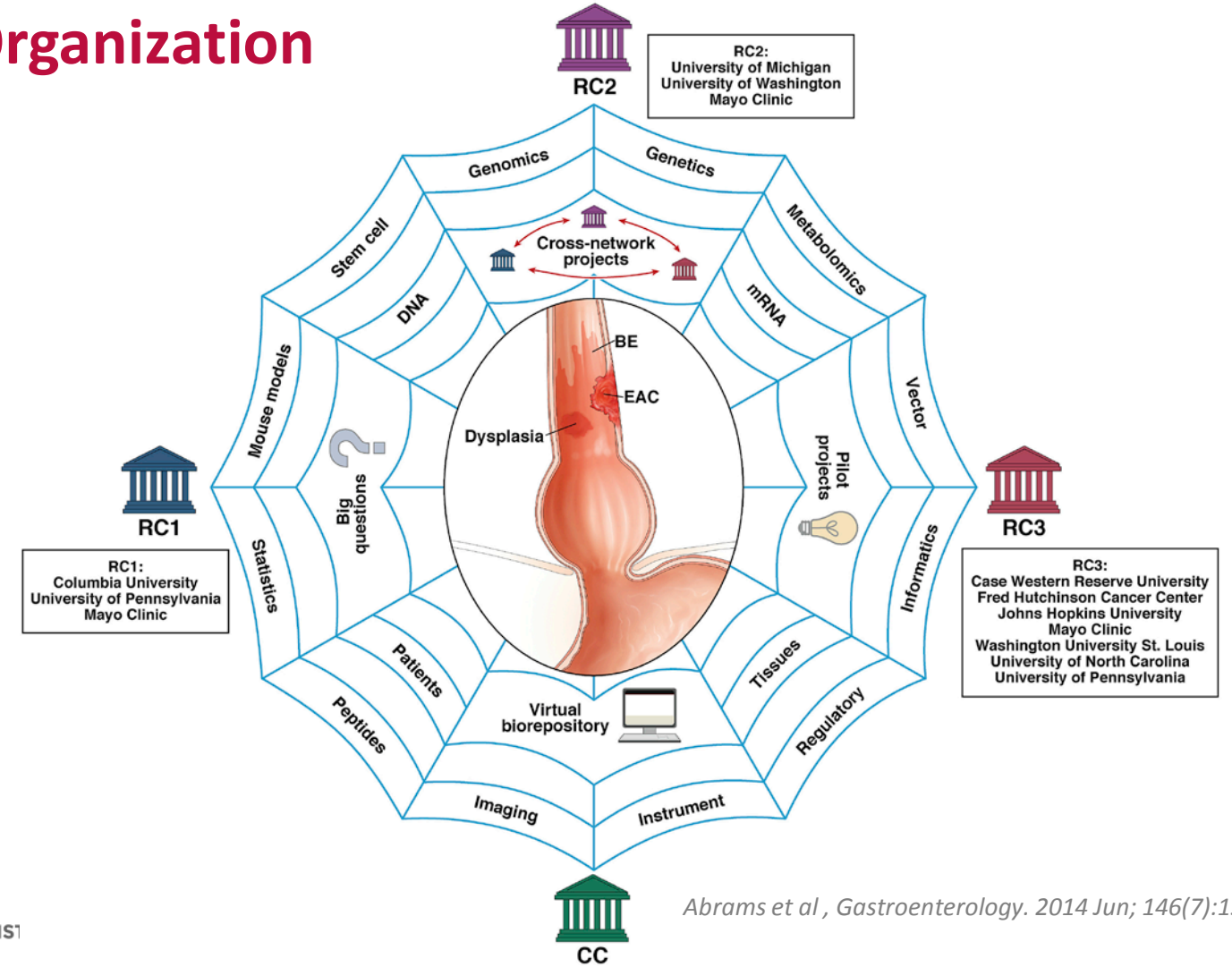
Esophageal Adenocarcinoma

- **Highly morbid and highly lethal cancer**
- **Unexplained dramatic rise in incidence and mortality**
- **BE confers increased risk**
  - **~ 11-30 fold greater than average risk**

  BUT
  - **80-90% of EA cases have no prior diagnosis of BE**

Hvid-Jensen F et al, NEJM 2011; 365:1375
Dulai GS et al, Gastroenterology 2002; 122:26

BETRNet Organization



Abrams et al , Gastroenterology. 2014 Jun; 146(7):1586–1590

From Discovery to Validation Through Team Science

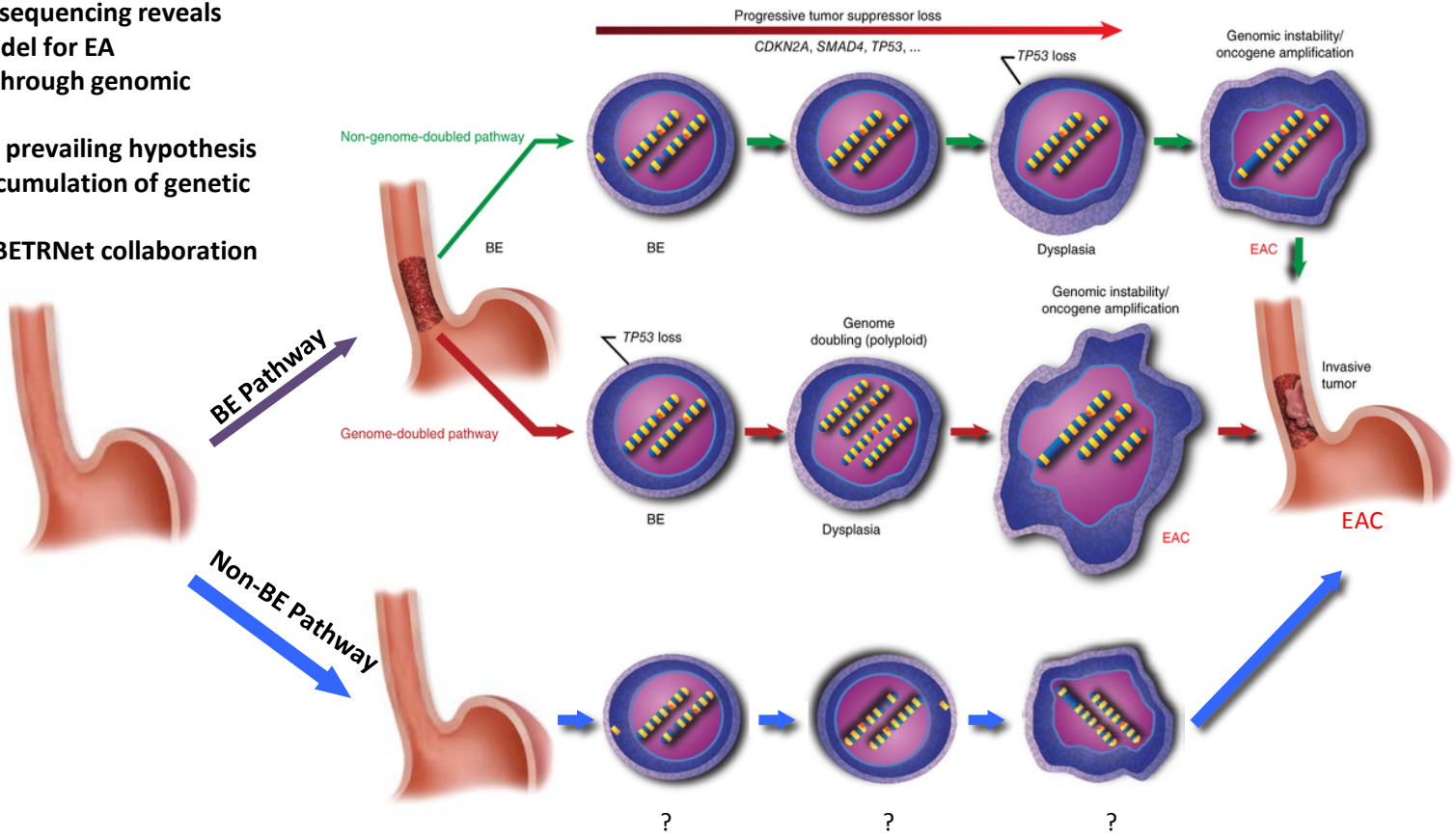
- **First transgenic (L2-IL-1β) mouse model of Barrett's-like metaplasia with multiple tumors at 12 months - developed by RC1**
  - BE/EA may arise from a stem/progenitor cell in the gastric cardia; this model challenges the dominant thinking in the field about the origin of BE/EA
  - BE gene signature more closely resembles cardia than squamous epithelium
- **Accelerated validation of the mouse model through the consortium**
  - Testing of chemopreventives (e.g., statins, obeticholic acid) in **RC2**
  - Validation of imaging markers for high grade dysplasia and EA (e.g., EGFR, Transglutaminase 2) in **RC3**

From Discovery to Validation Through Team Science (cont'd.)

- **Protective role of GSTT2 gene in African American esophagus**
  - Aimed to explain the increased prevalence of EA in Caucasians versus African Americans (ratio 4-6:1)
  - GSTT2 enzyme has a protective role against oxidative damage; however, in Caucasian GSTT2 is less expressed
- **Study made possible by combining rare esophageal cancer specimens from multiple BETRNet institutions**
- **Study completed and manuscript in preparation**

From Discovery to Validation Through Team Science (cont'd.)

- **Whole-exome sequencing reveals alternative model for EA development through genomic doubling**
- **Challenges the prevailing hypothesis of stepwise accumulation of genetic mutations**
- **Supported by BETRNet collaboration**



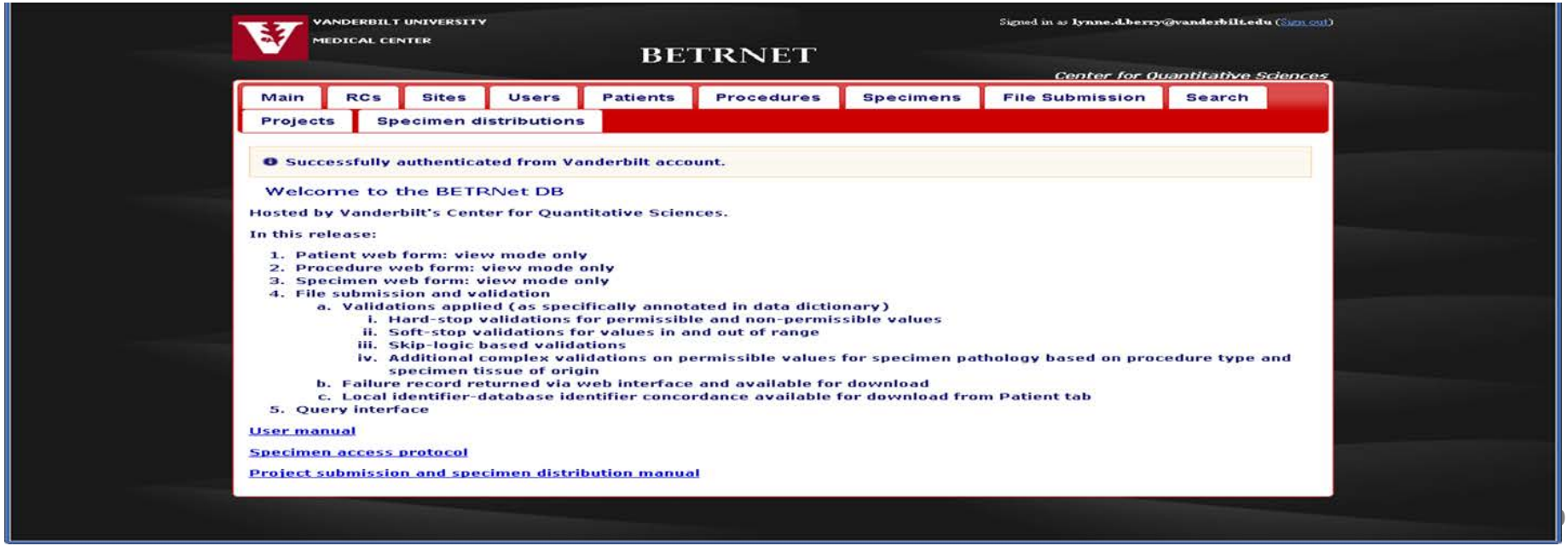
Stachler et al., 2015, Nature Genetics 47:1047

BETRNet Coordinated Outreach

- **Pilot projects with flexible funds to exploit emerging ideas advertised to outside investigators**
- **Cross-BETRNet focused sessions at national and international meetings included outside investigators**
- **Leading experts invited to BETRNet Steering Committee meetings**
- **Publications in major journals**

Patient Registry-Virtual Biorepository

- Access to specimens available through collaboration with BETRNet
- Review of proposals by an access committee
- 3901 unique specimens available as of November 2015
- Current revision to the PR-VR “public face” for easy access by the larger scientific community



BETRNet Program Evaluation
(Performed During Year 4)

- **RFA provided the necessary infrastructure to break down silos and support collaborative research to synergize science and accelerate opportunities for translational studies**

- **BE could be a model for understanding the development of other adenocarcinomas with unknown or inaccessible precursors**

- **Noted Significant Accomplishments**
  - EGFR probe with great potential for clinical use
  - Epigenetics and exome sequencing- an important foundation for future application
  - Registry-tissue repository - exceptionally valuable for a wide range of research studies
  - Cross-Center collaborations
  - Interactions with other NCI-supported entities such as the EDRN and CISNET

BETRNet Program Renewal (RFA Reissuance)

- **Research Centers (U54)**

  Multi-institutional, trans-disciplinary research groups to support:

  - Well-defined and NCI coordinated platform to advance research on a rare cancer
  - Collaborative accrual of sufficient cohorts/specimens that could not be collected at a single institution
  - Collaborative approach to new research directions and expertise sharing to permit adequate hypothesis testing (lesson learned)

- **Coordinating Center (U24)**

  - Administration of the consortium and continued expansion of the virtual biorepository

- **NCI Staff**

  - Active role in program organization, management, and performance evaluation to maximize integration and coordination of the complex U54 research structure with diverse scientific areas
  - Partnership with BETRNet investigators to prioritize and support research and outreach activities

Research Questions - New RFA

Cell of Origin

- Biology and development of esophageal stem cells and whether they are slow dividing cells or proliferative progenitors
- Effects of acid and inflammation on esophageal stem cells and their modulation by preventive agents
- Role of esophageal or other stem cells in the development of EA

Genomics of EA

- Impacts of spatial distribution of genetic alterations in BE on the evolution of EA
- The genomics of tumor heterogeneity and tumor plasticity and their impacts on the progression of EA
- The genomics of obesity and their effects on the risk of EA to inform molecular targeting for chemoprevention

Research Questions (continued)

Microbiota

- Alterations in BE and EA microbiota, their role in BE-EA transition and potential modulation for cancer prevention

Technologies and Models

- New technology for minimally invasive screening and surveillance

- Models such as engineered mice, PDX models, cell lines, and organoids that could provide a platform for understanding human esophageal epithelial transformation

Proposed Budget

Set aside request: $5.5 million in total costs (TC) per year for 5 years

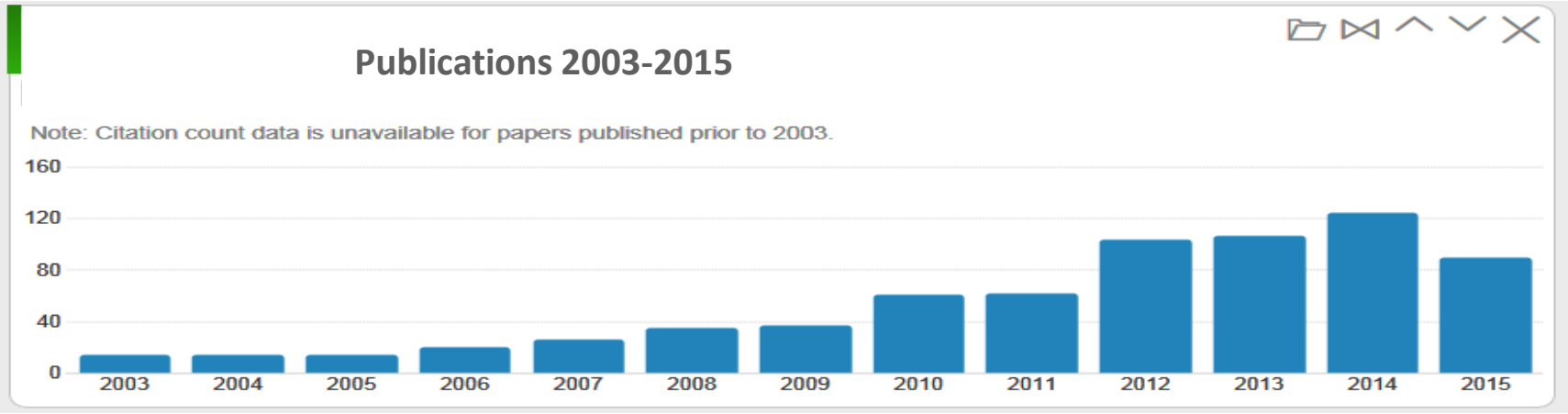
- **4 Research Centers**
  - $1.28 million TC per year each
- **1 Coordinating Center**
  - $375,896 TC per year
- **Invited speakers/small workshops**
  - $15,000 per year (administered by DCB - DCP)

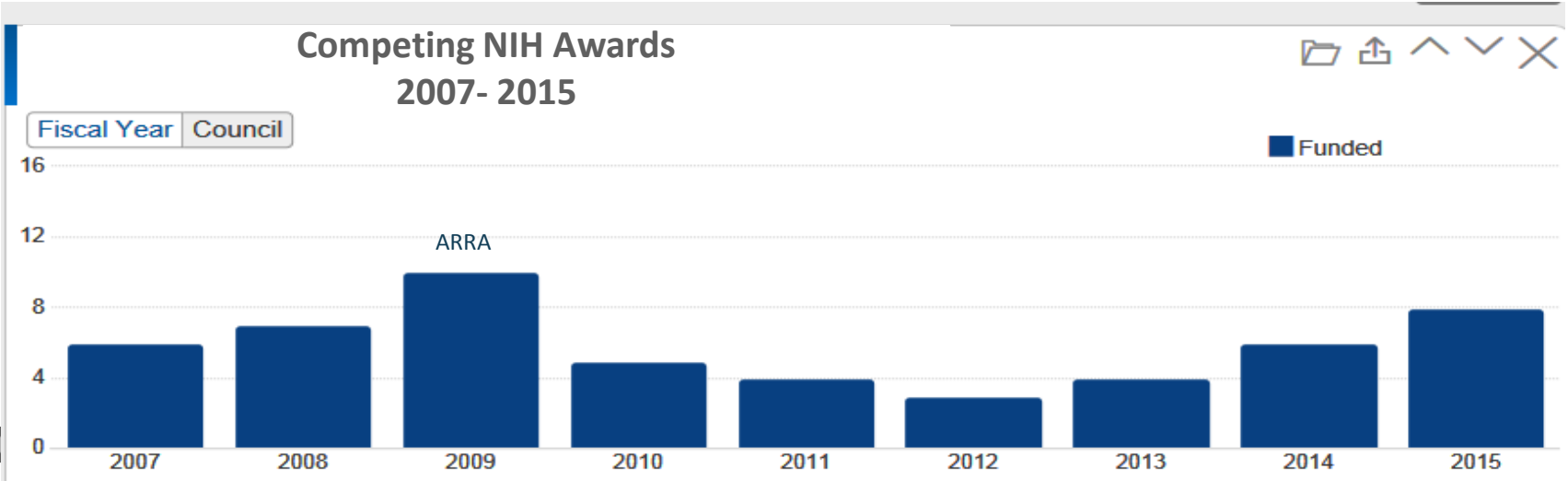
- **Total requested set aside for entire project period:**
  - **$27.6 million**

Portfolio Analysis - Fiscal Year 2014

- **NCI Extramural: ~ $17.2 million in total costs (TC)**
  - BETRNet, R01s, U01s and P01
- **NCI Intramural: $670,804 TC**
- **Other NIH institutes: $2.2 million TC**
  - K awards, some R01s
- **No existing multi-disciplinary collaborative programs**

Correlation of BETRNet (2011-2105) With the Landscape of EA Research





Program Evaluation Metrics (New Program)

- **Detailed scientific understanding of EA formation (years 1-4)**
  - Validation of the initial cell of origin findings in animal models and humans
  - Validation of the genomic doubling hypothesis underlying the molecular risk for EA formation
  - Sharing of scientific expertise and valuable specimens to tackle these research questions
  - Publication of the team research findings

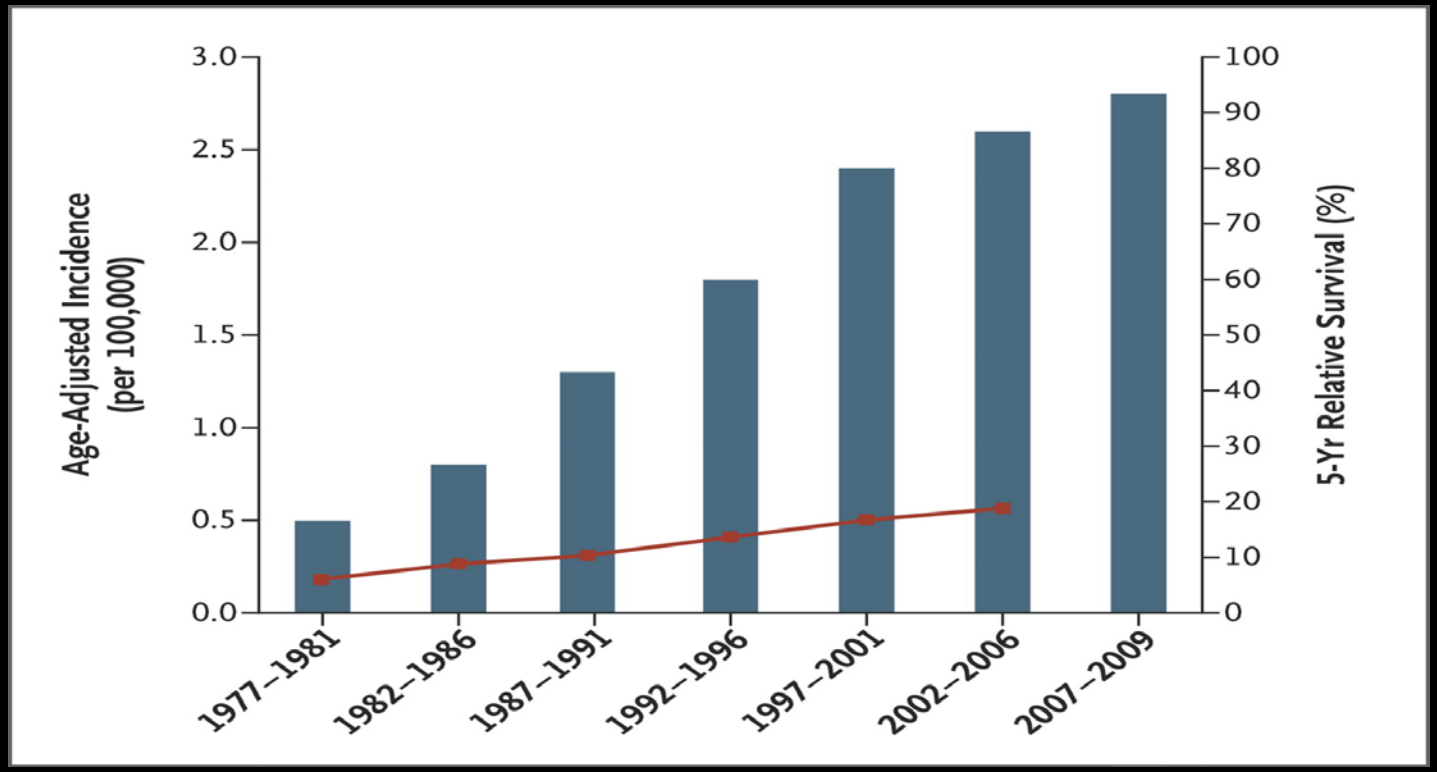
- **Improved PR-VR availability to the larger scientific community (years 1-5)**
  - Enhanced PR-VR accessibility for review by the larger scientific community (year 1)
  - Promotion of specimens availability for collaborative research studies (years 1-5)
  - Invitation of outside investigators to contribute specimens for collaborative research studies (years 1-5)

- **New research tools and technologies for patient management (years 1-5)**
  - Development of non-endoscopic and imaging devices for screening and surveillance
  - Development and validation of biomarker for risk stratification
  - Development of chemopreventive approaches

- **Model organisms, GWAS, data and resource sharing (according to NIH policies) (years 3-5)**
  - Links to data public sites available through the Coordinating Center website
  - Links to publications from outside investigators utilizing the resources

- **Questions?**

Temporal Trends in Incidence Rates and Survival Rates for Esophageal Adenocarcinoma



Rustgi AK, El-Serag HB. N Engl J Med 2014;371:2499-2509.

The NEW ENGLAND JOURNAL of MEDICINE

Additional BETRNet Accomplishments

- **First-in-human trial**
  - **Image guided endoscopic biopsy using fluorescent peptides to bind with cell surface markers (e.g., epidermal growth factor receptor)**
  - **Aberrant *vimentin* methylation - common in upper GI neoplasia**
    - Novel non-endoscopic device study is underway

Additional Program Evaluation Criteria

- Collaboration and participation in new pilot studies within the network and outside the network
- Sharing of human specimens between centers to answer collaborative research questions
- New grant applications from cross-BETRNet studies
- New models and resources to be shared with the scientific community
- New research tools & applications for patient management
- Active participation in Steering Committee meetings, focused scientific committees, and other BETRNet activities
- Publication of collaborative research findings