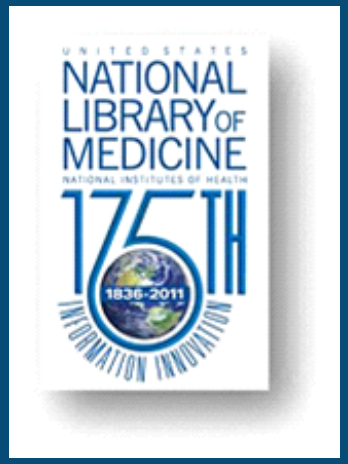

Semantic MEDLINE: An Advanced Information Management Application for Biomedicine

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Lister Hill National Center
for Biomedical Communications

Access to online text

- Document retrieval systems
  - Document retrieval systems
  - Google
  - PubMed
  - Tailored for biomedical information
- Technology: Manipulate text strings
  - Technology: Manipulate text strings
    - Frequency of occurrence

Access to online text

- Document retrieval systems
  - Google
  - PubMed for biomedical information
- Technology: Manipulate text strings
  - Frequency of occurrence
  - Distribution patterns
  - No access to meaning

Emerging applications

- Text mining
  - Task-driven extraction of facts
  - Observe trends
- Connect text and structured data
- Question answering
- Literature-based discovery
  - Research assistance

Emerging applications

- Text mining
  - Task-driven extraction of facts
  - Observe trends
- Connect text and structured data
- Question answering
- Literature-based discovery
  - Research assistance
- Require more effective language processing

Automatic semantic interpretation

- Augment document retrieval systems
- Manipulate information
  - Not just documents
- Bridge the gap between
  - Language (text)
  - Meaning
- Summarize and visualize information
  - In the biomedical domain

Automatic semantic interpretation

- Augment document retrieval systems
- Manipulate information
  - Not just documents
- Bridge the gap between
  - Language (text)
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    Semantic MEDLINE

Semantic MEDLINE

PubMed

MEDLINE citations

Natural language processing

Semantic relationships

Automatic summarization

Graphical summary

Enhanced access to biomedical research literature

Extract relationship from text

TI - Exemestane after non-steroidal aromatase inhibitors for post-menopausal women with advanced breast cancer. AB - A retrospective analysis was performed on 31 consecutive locally advanced or metastatic breast cancer patients who commenced exemestane 25mg/d orally following previous treatment with Tamoxifen and a non-steroidal third-generation aromatase inhibitor (AI). Patients were seen 3 monthly until clinical or radiological disease

… Exemestane after non-steroidal aromatase inhibitor for post-menopausal women with advanced breast cancer

inhibitors and tamoxifen in the treatment of hormone-dependent breast cancer. AB - Within the past 2 years three separate groups reported marked improvements in relapse-free survival when trastuzumab was added to adjuvant chemotherapy in patients with HER2-overexpressing breast cancer. Notwithstanding the significance of this molecular target, the discovery of the estrogen receptor (ER) may be of even greater importance. Although tamoxifen has long been considered the hormonal therapy of choice for patients with estrogen-responsive breast cancer, accumulating clinical data suggest the new generation of aromatase inhibitors (AIs) is more effective and less toxic. With the availability of new information, guidelines have been updated and reformulated regarding the use of AIs as first-line hormonal therapy in postmenopausal women with ER-positive breast cancer. This paper, a product of the ongoing advances in oncology, incorporates two distinct, yet important, features of oncology; first, clinical concepts related to hormone-dependent breast cancer and second, pharmacoeconomic evaluation of the antiestrogen tamoxifen and the new generation of antiaromatase agents. TI - An alpha-fetoprotein-derived peptide reduces the uterine hyperplasia and increases the antitumour effect of tamoxifen. AB - Tamoxifen (Tam) is effective for the treatment and prevention of breast cancer. However, it has toxic drawbacks and has limited-duration utility because, over time, human tumours become refractory to Tam. Recently, a new nontoxic peptide, alpha-fetoprotein-derived peptide (AFPep) has been proposed for the treatment and prevention of breast cancer. The purpose of this paper is to determine whether combining AFPep with Tam would increase efficacy and reduce toxicity in experimental models of breast cancer. Low doses of AFPep and Tam were more effective in combination than either agent alone against breast cancer growth in cell culture, in tumour-xenografted mice, and in carcinogen-exposed rats. alpha-Fetoprotein-derived peptide interfered with Tam-induced uterine hyperplasia in immature mice, and showed no toxic effects. Unlike Tam, AFPep did not inhibit binding of oestradiol (E(2)) to oestrogen receptor (ER). Thus, these two agents utilise different mechanisms to interfere with ER functionality, yet work cooperatively to reduce breast cancer growth and alleviate Tam's troubling toxicity of uterine hyperplasia and appear to be a rational combination for the treatment of ER-positive breast cancer.British Journal of Cancer (2007) 97, 327-333. TI - Adjuvant trastuzumab in the treatment of HER-2-positive early breast cancer: a meta-analyses of published randomized trials. AB - ABSTRACT: BACKGROUND: Breast cancer is the most common cancer in women in the U.S. and western Europe. Amplification of the her-2/neu gene occurs in approximately 25% of invasive ductal carcinomas of the breast. The first HER-2/neu-targeted approach to reach the clinic was trastuzumab, a humanized monoclonal antibody directed against the extracellular domain of the HER-2/neu protein. Trastuzumab therapy prolongs the survival of patients with metastatico HER-2/neu-overexpressing breast cancer when combined with chemotherapy and has recently been demonstrated to lead to dramatic improvements in disease-free survival when used in the adjuvant therapy setting in combination with or following chemotherapy. Here, we performed a meta-analyses of completed clinical trials of adjuvant trastuzumab in the adjuvant setting. Survival, recurrence, brain metastases, cardiotoxicity and directions for future research are discussed. METHODS: A meta-analysis of randomized controlled trials (RCT) was performed comparing adjuvant trastuzumab treatment for HER2-positive early breast cancer (EBC) to observation. The MEDLINE, EMBASE, CANCERLIT and Cochrane Library databases, and abstracts published in the annual proceedings were systematically searched for evidence. Relevant reports were reviewed by two reviewers independently and the references from these reports were searched for additional trials, using guidelines set by QUOROM statement criteria. RESULTS: Pooled results from that five randomized trials of adjuvant Trastuzumab showed a significant reduction of mortality (p0.00001), recurrence (p0.00001), metastases rates (p0.00001) and second tumors other than breast cancer (p=0.007) as compared to no adjuvant Trastuzumab patients. There were more grade III or IV cardiac toxicity after trastuzumab (203/4555 = 4.5%) versus no trastuzumab (86/4562 = 1.8%). The likelihood of cardiac toxicity was 2.45-fold higher (95% CI 1.89 - 3.16) in trastuzumab arms, however that result was associated with heterogeneity. The likelihood of brain metastases was 1.82-fold higher (95% CI 1.16 - 2.85) in patients who received trastuzumab. CONCLUSION: The results from this meta-analysis are sufficiently compelling to consider 1 year of adjuvant trastuzumab treatment for women with HER-2-positive EBC based on the risk: benefit ratio demonstrated in these studies. Adequate assessment of HER-2/neu status is critical, and careful cardiac monitoring is warranted because of cardiac toxicity. Clinical trials should be designed to answer unsolved questions. TI - Prognostic and Predictive Value of Centrally Reviewed Expression of Estrogen and Progesterone Receptors in a Randomized Trial Comparing Letrozole and Tamoxifen Adjuvant Therapy for Postmenopausal Women With Early Breast Cancer: Results From the BIG 1-98 Collaborative Groups. AB - PURPOSE: To evaluate locally versus centrally assessed estrogen (ER) and progesterone (PgR) receptor status and the impact of PgR on letrozole adjuvant therapy compared with tamoxifen in postmenopausal women with early breast cancer. PATIENTS AND METHODS: Breast International Group (BIG) 1-98 randomly assigned 8,010 patients to four arms comparing letrozole and tamoxifen with sequences of each agent. The Central Pathology Office received material for 6,549 patients (82%), of which 79% were assessable (6,291 patients). Prognostic and predictive value of both local and central hormone receptor expression on disease-free survival (DFS) were evaluated among 3,650 assessable patients assigned to the monotherapy arms. Prognostic value and the treatment effect were estimated for centrally assessed ER and PgR expression levels using the Subpopulation Treatment Effect Pattern Plot. RESULTS: Central review confirmed 97% of tumors as hormone receptor-positive (ER and/or PgR >/=10%). Of 105 tumors locally ER-negative, 73 were found to have more than 10% positive cells, and eight had 1% to 9%. Of 6,100 tumors locally ER positive, 66 were found to have no staining, and 54 had only 1% to 9%. Discordance was more marked for PgR than ER. Patients with tumors reclassified centrally as ER-negative, or as hormone receptor-negative, had poor DFS. Centrally assessed ER and PgR showed prognostic value. Among patients with centrally assessed ER-expressing tumors, letrozole showed better DFS than tamoxifen, irrespective of PgR expression level. CONCLUSION: Central review changed the assessment of receptor status in a substantial proportion of patients, and should be performed whenever possible in similar trials. PgR expression did not affect the relative efficacy of letrozole over tamoxifen. TI - Drug insight: breast cancer prevention and tissue-targeted hormone replacement therapy. AB - The first-generation selective estrogen receptor modulator (SERM) tamoxifen has been the mainstream hormone therapy in breast cancer. Tamoxifen benefits all stages of the disease, but its use increases the risk of uterine cancer and thromboembolic events and it can only be administered for 5 years. Aromatase inhibitors are superior to tamoxifen at advanced stages of disease and as adjuvants; however, because they increase fractures, aromatase inhibitors are unlikely to be used to prevent disease. Raloxifene, a second-generation SERM, leads, like tamoxifen, to approximately 50% fewer cases of invasive breast cancer in high risk women, with a lower incidence of thromboembolic events. Several other SERMs are in development to improve tissue specificity, efficacy and tolerance. Raloxifene shows protection against vertebral fractures similar to bisphosphonates; however, no significant effect has been observed on nonvertebral fractures. Many SERMs are in development for prevention and treatment of osteoporosis. As breast cancer metastasizes early and advanced disease cannot be cured, prevention is essential. To avoid the concerns about the use of traditional hormone replacement therapy, dehydroepiandrosterone--a tissue-targeted precursor of sex steroid formation--offers hope of a physiological tissue-targeted hormone replacement that, combined with a SERM, would simultaneously prevent breast and uterine cancer. TI - Comparative economic analysis of aromatase inhibitors and tamoxifen in the treatment of hormone-dependent breast cancer. AB - Within the past 2 years three separate groups reported marked improvements in relapse-free survival when trastuzumab was added to adjuvant chemotherapy in patients with HER2-overexpressing breast cancer. Notwithstanding the significance of this molecular target, the discovery of the estrogen receptor (ER) may be of even greater importance. Although tamoxifen has long

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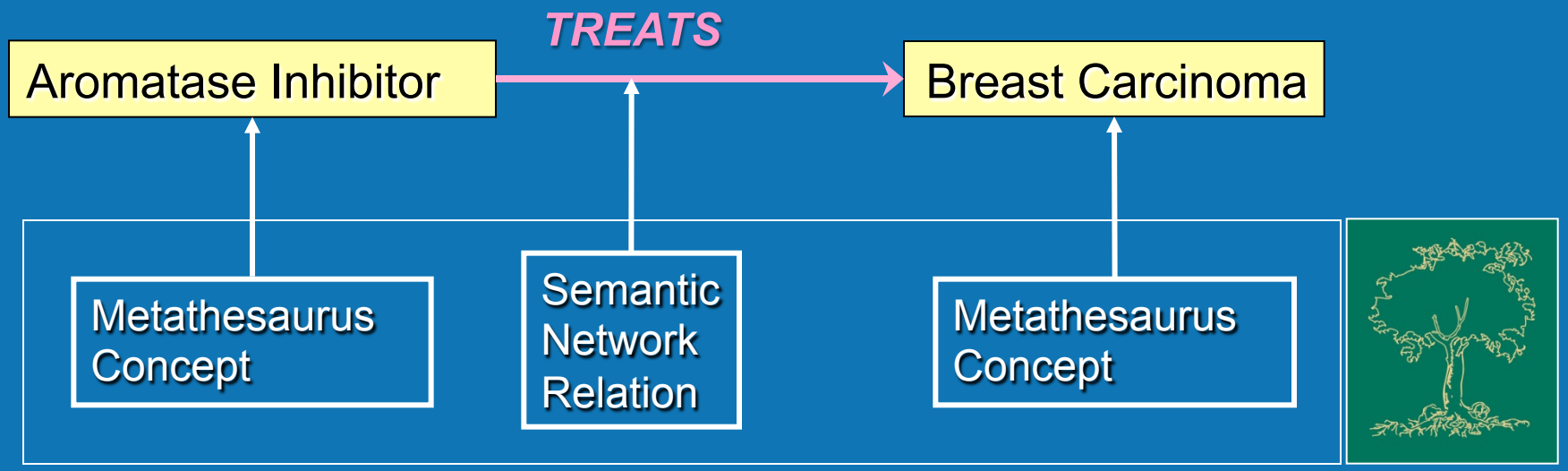


Unified Medical Language System

Unified Medical Language System

- Developed by National Library of Medicine
- SPECIALIST Lexicon
  - Linguistic information
- Metathesaurus
  - Biomedical concepts
- Semantic Network
  - Relationships between concepts

Metathesaurus concept

- Concept name
  - Arthroplasty
- Synonyms
  - Reconstruction of joint
  - Repair of joint …
- Semantic type
  - Therapeutic or Preventive Procedure

Semantic Network relationships

Therapeutic or Preventive Procedure USES Medical Device

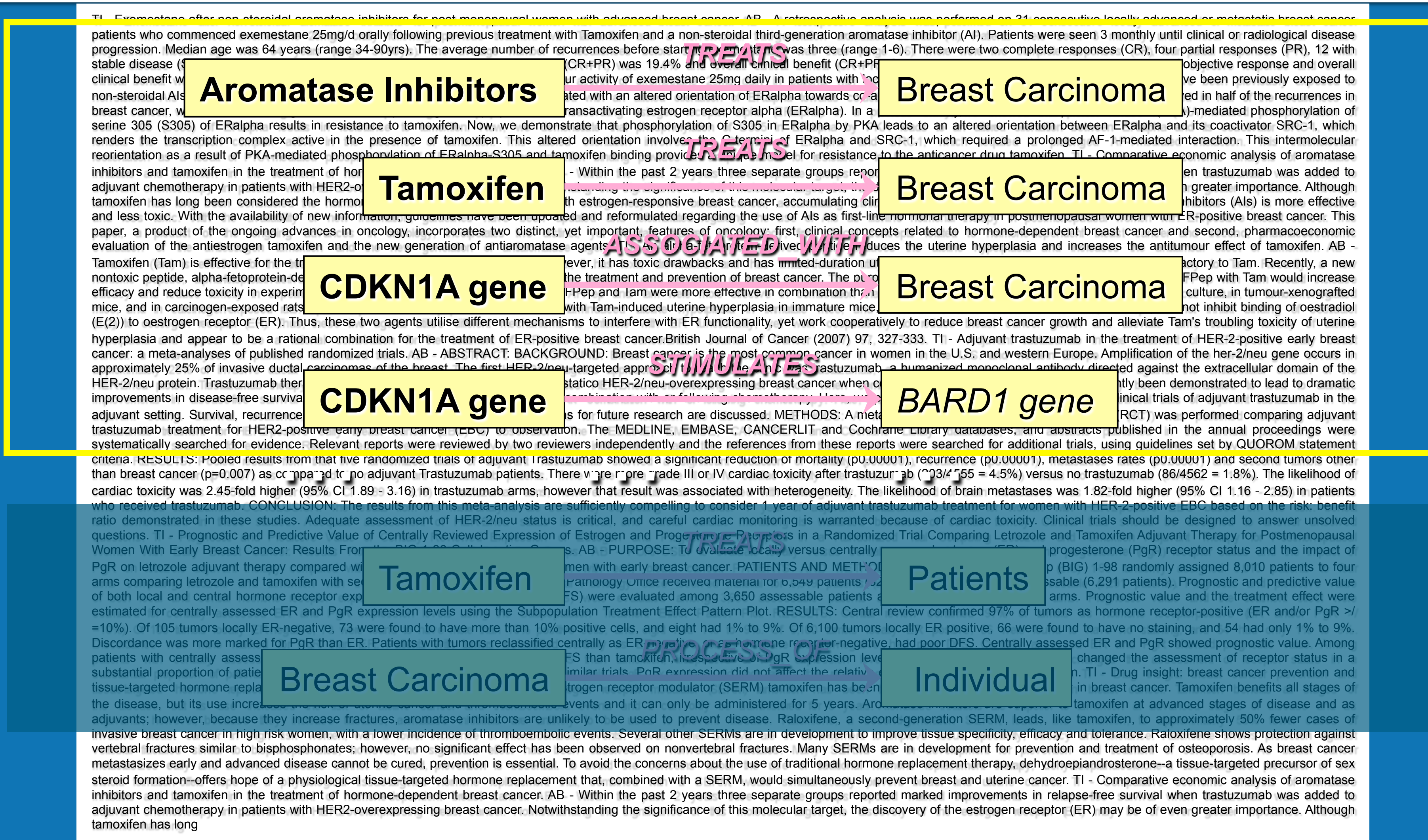
Pharmacologic Substance TREATS Disease or Syndrome

Body Location or Region LOCATION_OF Biologic Function

Disease or Syndrome OCCURS_IN Population Group

Disease or Syndrome PROCESS_OF Organism

Semantic relationships from text



Domain coverage

- Initially developed for clinical medicine
- Extended to
  - Genetic etiology of disease
  - Substance interactions
  - Pharmacogenomics
- Working on
  - Influenza epidemic preparedness
  - Climate change and health
  - Health promotion
  - Biomedical knowledge processing

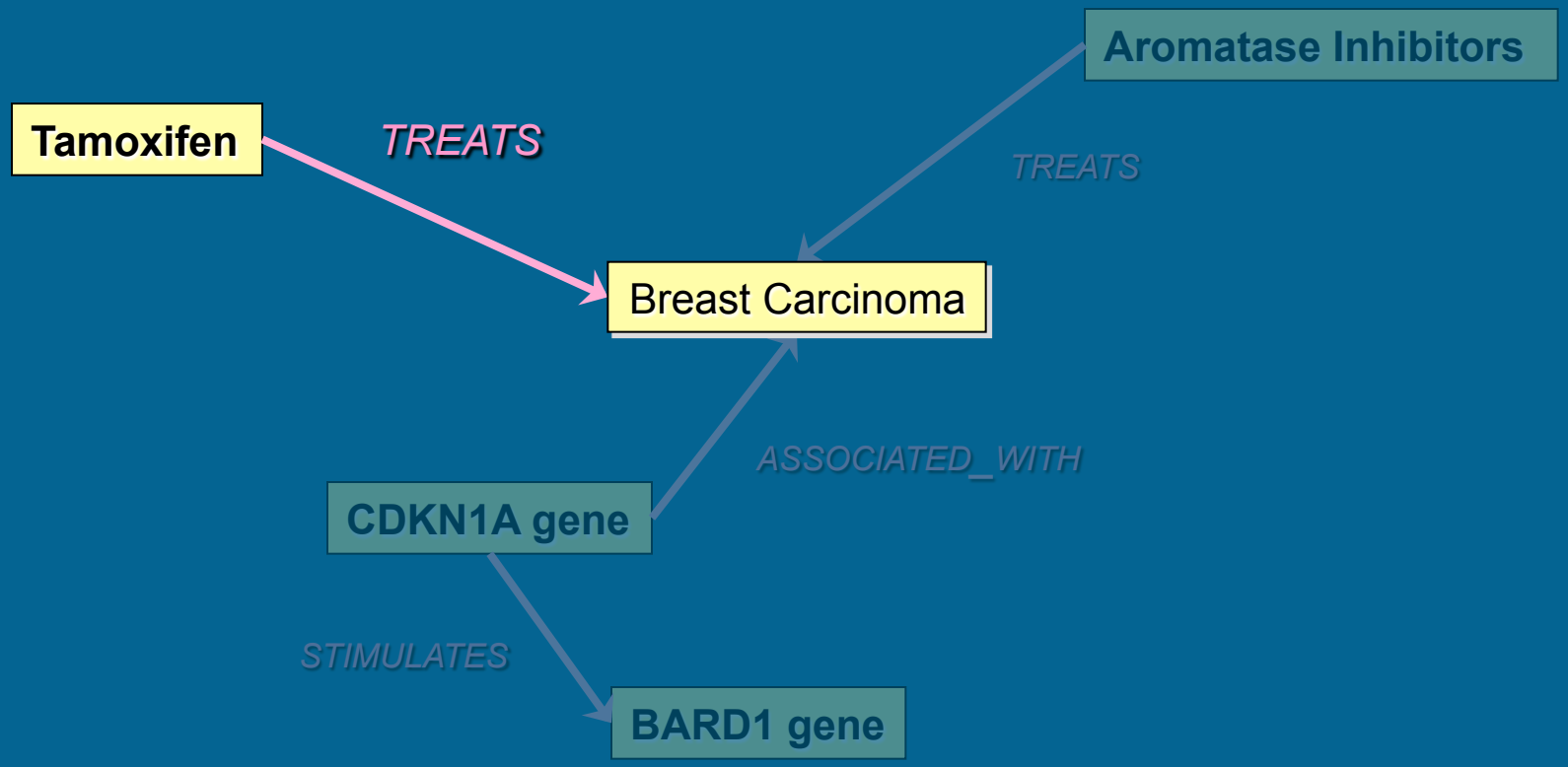
Several evaluations

- Focused on biomedical subdomains, e.g.
  - Clinical treatment
  - Genetic etiology of disease
  - Pharmacogenomics
- Overall
  - Precision is around 75% (lower for molecular biology)
  - Recall is around 60%

Semantic database

- MEDLINE (National Library of Medicine)
  - Bibliographic database of the biomedical research literature
  - More than 21million citations (1940s to present)
- Semantic relationships extracted
  - 57 million (through 03/31/2012)
- Made available to the research community
  - SQL database
  - RDF triples

Information visualization



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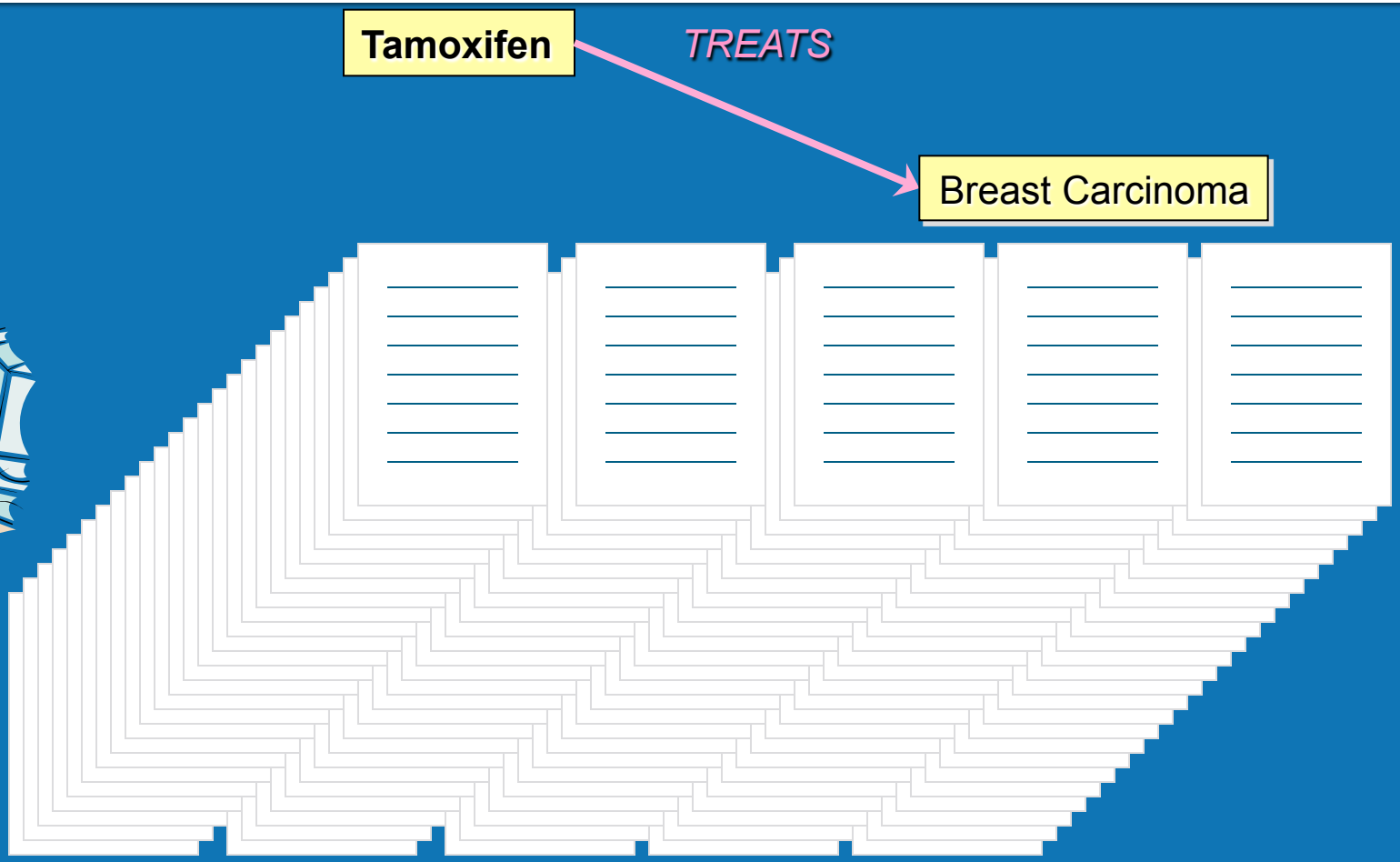

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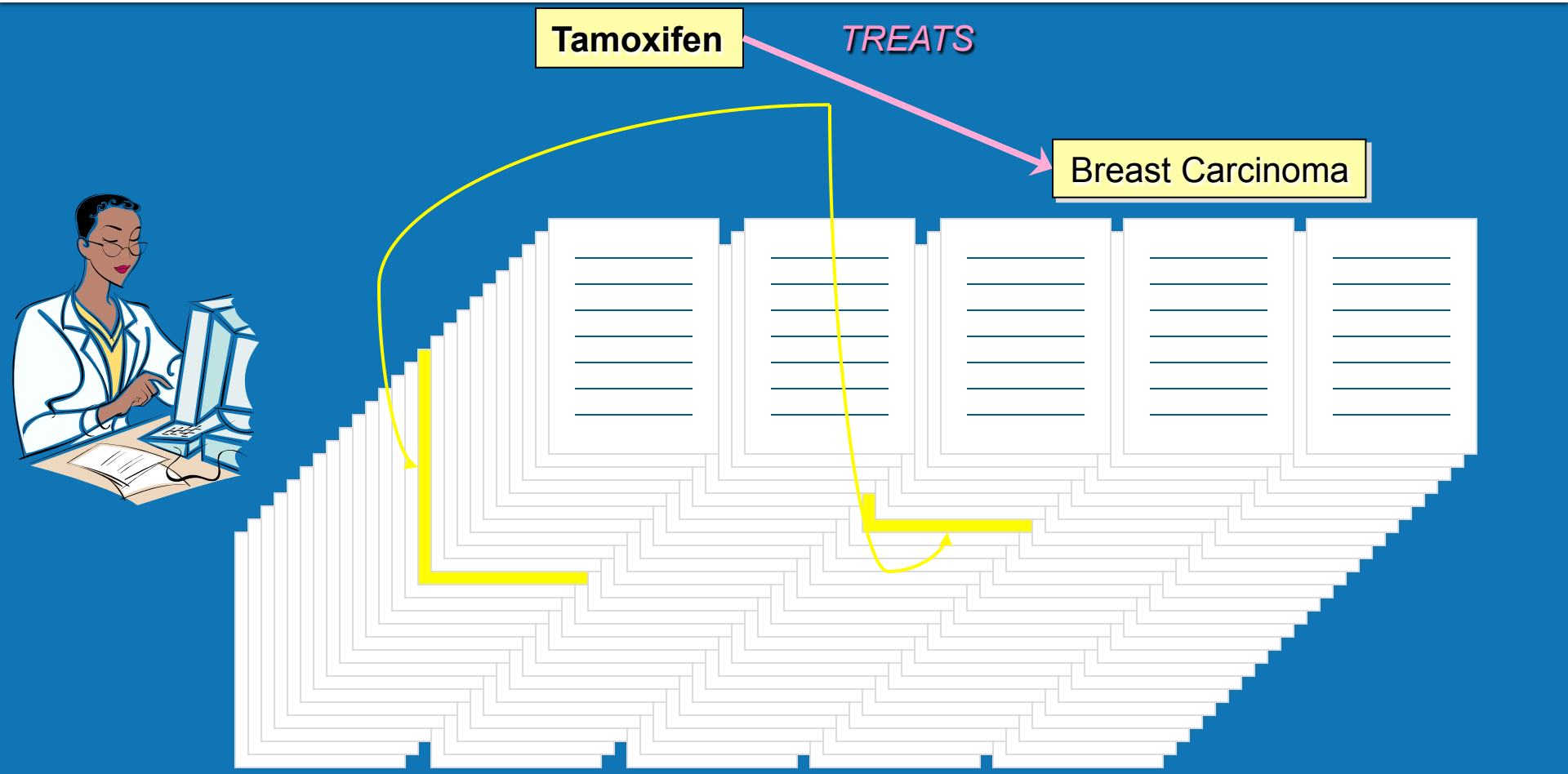
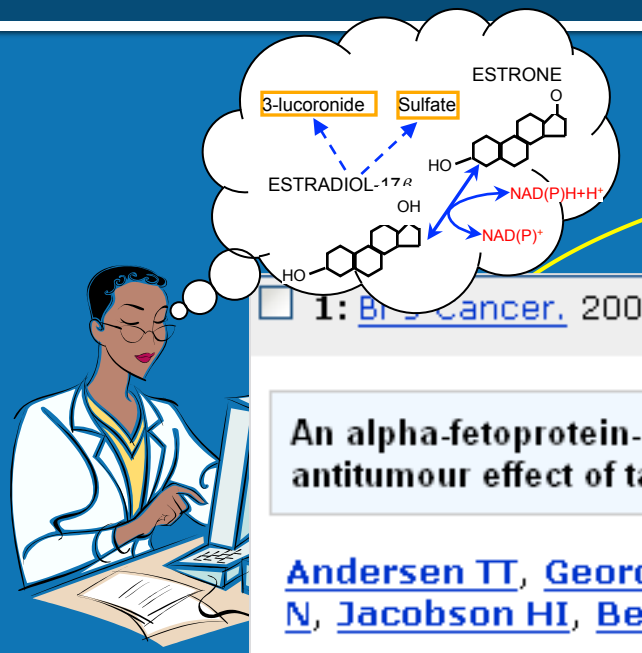


Conduct research



Tamoxifen *TREATS* **Breast Carcinoma**

1: Br J Cancer. 2007 Aug 6;97(3):327-33. Epub 2007 Jul 17.

An alpha-fetoprotein-derived peptide reduces the uterine hyperplasia and increases the antitumour effect of tamoxifen.

Andersen TT, Georgekutty J, Defreest LA, Amaratunga G, Narendran A, Lemanski N, Jacobson HI, Bennett JA.

Center for Cardiovascular Sciences, Albany Medical College, Albany, NY 12208, USA. anderst@mail.amc.edu

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Exploiting the technology

- Manipulate online information
  - Summarize
  - Visualize
  - Connect text to structured data
- Facilitate literature-based discovery for:
  - Research assistance
  - Observing trends
  - Support for decision making
    - Portfolio analysis

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