Humanistic and Economic Burdens of Triple-Negative Breast Cancer: A Literature Review

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Background
- Triple-negative breast cancer (TNBC) is a complex form of breast cancer lacking expression of estrogen receptors, progesterone receptors, and human epidermal growth factor receptor.
- Approximately 10-15% of breast carcinomas are of the TNBC subtype, and although triple-negative tumors have good initial response to chemotherapy, disease-free survival is short. Patients with TNBC generally have lower five-year survival than other breast cancer types, and relapsed cases have particularly poor prognosis.
- There has been little therapeutic progress during past decades, and chemotherapy remains the standard of care. Recent advances in understanding biological processes in TNBC have revealed novel targets including poly ADP-ribose polymerase (PARP) and immune checkpoints, and trials of monotherapy and combination regimens for new treatments are underway.
- Breast cancer imposes large quantity of significant impacts on physical, psychological, and emotional functioning, and is estimated to have the highest cost for any single cancer type.1 A recent literature review suggests that while there exists an emphasis on literature of burden of disease more broadly, literature specific to TNBC economic burden is limited.2
- Considering its substantial humanistic and economic burden, and its aggressive and difficult-to-treat nature, research into humanistic and economic impacts of TNBC is required to inform clinicians, patients, and payers.

Objective
- To summarize available data related to the humanistic and economic burden of triple-negative breast cancer (TNBC).

Methods
- A systematic literature review was conducted to establish clinical, medical, and economic databases using a range of Medical Subject Headings (MeSH) terms and key words.
- Databases (MEDLINE, Embase, Econlit, and National Health Services Economic Evaluation Database (NHS EED), were searched for English language publications from 2010 (economic burden) up to July 2018. Conference abstracts were searched through Embase database and included American Society of Clinical Oncology (ASCO) European Society for Medical Oncology, and San Antonio Breast Cancer Symposium published between January 2016 and the end of 2018. The 2018 ASCO conference proceedings were not available through Embase at the time of the search, and therefore acquired manually by searching the PDF files containing all abstracts from the conference website.
- Inclusion was based on the following RCDO criteria:
  - Population: adult females with TNBC
  - Interventions: any systemic pharmacotherapy given in any of:
    - First-line or second-line and beyond treatment for metastatic stage (Stage IV)
    - Neoadjuvant and adjuvant treatment for early stages (Stage I-II)
  - Comparator(s): any or none
  - Outcomes of interest:
    - Humanistic outcomes of interest such as health-related quality of life (HRQoL); physical, emotional and social functioning; fatigue, pain, emotional distress; well-being, or participation in employment.
    - Economic outcomes of interest such as resource utilization cost, burden of illness, incremental cost-effectiveness, and cost-utility.
- Quality of research and reporting was approved for full publications. Observational burden-of-disease publications were approved using the principles of the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach.

Search Results and Characteristics of Included Studies
- The search identified 410 publications for humanistic (Figure 1) and 506 publications for the economic burden (Figure 2) of TNBC. Following title, abstract, and full-text screening, 34 publications were identified for the humanistic and 6 for the economic burdens, respectively.
- Humanistic burden study characteristics are available in Table 1 for the 11 studies of (34) that report patient-reported outcomes (PRO) and/or HRQoL measures for the TNBC population. The remaining 23 studies reported HRQoL outcomes, which were selected based on the relevant topics of assessment. (European Organization for Research and Treatment of Cancer Quality of life questionnaires QLQ-C30, QLQ-BR23, and EORTC Symptom Assessment Scales EQ-5D, Functional Assessment of Cancer Therapy – Breast-C30, and QLQ-BR23) and one using a phone questionnaire. In addition, we report PROs of patient-reported outcomes of other PRO measures such as functional health and wellbeing or fatigue, and are mentioned above used various tools including self-report, physician notes, structured interviews, and ad hoc questionnaires.
- Characteristics for the included economic studies are presented in Table 2. Recourse use/cost were reported in 41 economic burden studies, and 24 reported humanistic cost-effectiveness of systemic therapies for TNBC were reported in 1 study from France and 1 study from the UK.

Humanistic and Economic Burden Results
- Humanistic burden of TNBC studies showed that:
  - HRQoL is negatively impacted by systemic chemotherapy toxicity, which is the only recommended therapy for TNBC during the time of this literature review, and illustrates need for targeted therapy in TNBC.2
  - TNBC related to disease progression, with increased physical pain, trouble sleeping, decreased physical and sexual functioning, and acute distress.1
  - For metastatic disease manifested in the brain, cognitive function decreased.25
  - Higher rates of TNBC have been observed in women who are younger as compared to other types of breast cancer.
  - Elderly TNBC patients face challenges in accessing treatment. About half of Medicare metastatic TNBC patients do not receive chemotherapy in the real world, increasing humanistic burden of untreated disease.12
  - Humanistic burden of TNBC is greater in communities and countries with fewer treatment options and support infrastructure than large US urban centers. The situation is particularly difficult in the developing world, where shortages of resources are limited and fertility in the field is lacking. One of the few countries facing heightened burden of TNBC is India. A systematic review of TNBC rates in India by Sandhu et al.3 found that the overall prevalence could be as high as 31% (95% confidence interval, 27% to 35%) as contrasted to the usual 10-20% prevalence found in western countries.

Economic burden of TNBC studies showed that:
- Economic burden of TNBC studies were based on US American health care, or clinical registry data linked to claims data;4-11 and no studies reported administered out-of-pocket costs, insurance costs, or cost of adverse events management.
- For all types of resource use, TNBC patients had significantly higher utilization than patients that were compared with any single agent, chemotherapy, radiotherapy, symptomatic treatment alone, or asymptomatic control.12
- From a French health care system perspective, compared with paclitaxel alone, the incremental cost-effectiveness of bevacizumab+ paclitaxel compared to paclitaxel alone was $6,874 per quality-adjusted life year (QALY).12
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Overall, the assessment of the humanistic burden of TNBC is difficult due to lack of available data. No studies provided information out-of-pocket cost to patients and families, productivity losses, and other indirect costs that are relevant from a societal perspective. This review highlights the need for continuing research on humanistic and economic burdens of TNBC.

Disclosures
- This review was sponsored by Bristol-Myers Squibb

Table 1: Humanistic burden studies reporting HRQoL or PRO

<table>
<thead>
<tr>
<th>Author &amp; Year (Cronin 2018)</th>
<th>Title</th>
<th>Sample Source</th>
<th>Study Design</th>
<th>Measures</th>
<th>Patient Data Source</th>
<th>PRO reported</th>
</tr>
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<tbody>
<tr>
<td>Paganini K &amp; A (2017)</td>
<td>A First Cost-Effectiveness Analysis Based on Clinical Outcomes of a Randomized Phase 3 Trial: Paclitaxel vs. Paclitaxel + Palbociclib Among French Patients with Recurrent or Advanced Breast Cancer: Results of ECOG 2506</td>
<td>Pharmacoeconomic Analysis</td>
<td>Cross-sectional</td>
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<td>France</td>
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<td>Wei J (2016)</td>
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<td>Pharmacoeconomic Analysis</td>
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Table 2: Economic burden studies

<table>
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<tr>
<th>Author &amp; Year (Cronin 2018)</th>
<th>Title</th>
<th>Sample Source</th>
<th>Study Design</th>
<th>Measures</th>
<th>Country &amp; Currency</th>
<th>Year</th>
<th>Cost &amp; Cost-Effectiveness</th>
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Note: no qualifying papers were identified from EORTC for the NHS EED review.