Cancer Genetics

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Disclosure of Conflict(s) of Interest

- Leigha Senter, MS, CGC reported the following relevant financial relationships or relationships with ineligible companies of any amount during the past 24 months.
  - *Speaker's Bureau:* AstraZeneca

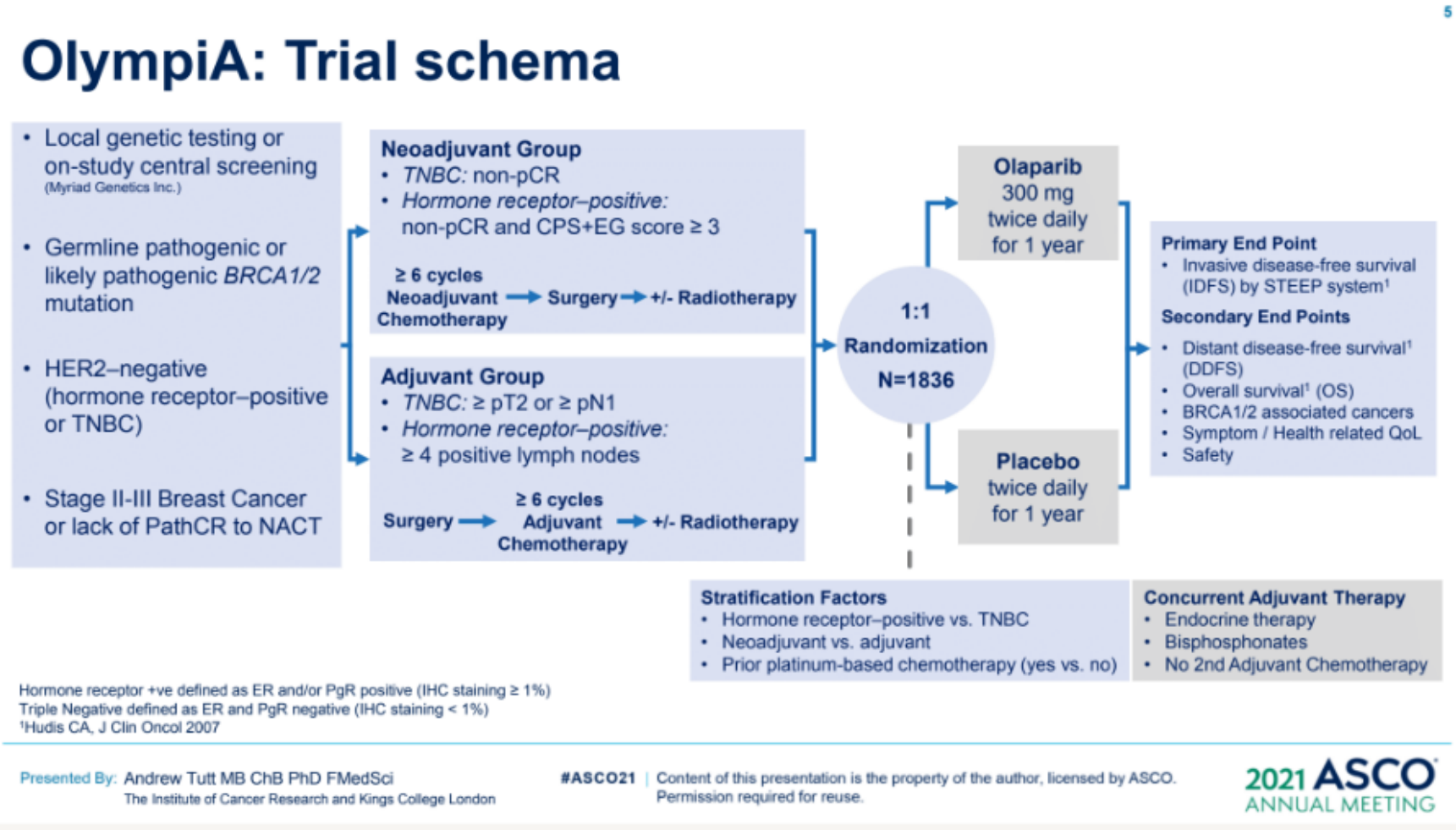
Learning objectives

- Review the results of the Olympia trial and their importance related to genetic testing in patients diagnosed with breast cancer
- Evaluate genetic testing outcomes in patients with prostate cancer
- Appreciate the limitations of direct-to-consumer (DTC) genetic testing in the context of oncology care

Brief background – BRCA1 and BRCA2

- Tumor suppressor genes
- Pathogenic variants (aka mutations) in these genes cause hereditary increased risk of cancer
  - Breast cancer: >60%
  - Ovarian cancer: up to 60% (BRCA1); up to 30% (BRCA2
  - Prostate cancer: up to 16% (BRCA1); up to 34% (BRCA2)
  - Male breast cancer (up to 9%), pancreatic cancer (up to 8%), melanoma
- BRCA1/2 play role in repair of double stranded DNA breaks
- PARP occurs in cells and plays a role in single stranded breaks
- When you inhibit PARP and double stranded breaks are also not repaired – leads to cell death

Plenary Session LBA1: OlympiA: A phase III, multicenter, randomized, placebo-controlled trial of adjuvant olaparib after (neo)adjuvant chemotherapy in patients with germline BRCA1/2 mutations and high-risk HER2-negative early breast cancer.



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- Enrolled female patients with germline (inherited) mutation in BRCA1/2 and HER2-negative breast cancer with high risk features
- Patients were randomized 1:1 to receive 1 year of oral PARPi (olaparib) or placebo
- The primary endpoint was invasive disease-free survival (IDFS) in the ITT population
- Unblinding was recommended because those in the PARPi arm received significant benefit at 2.5 years follow up (HR 0.58)
- Adjuvant OL following ACT or NACT significantly improved IDFS and DDFS with acceptable toxicity in pts with gBRCAm and high-risk HER2-negative EBC

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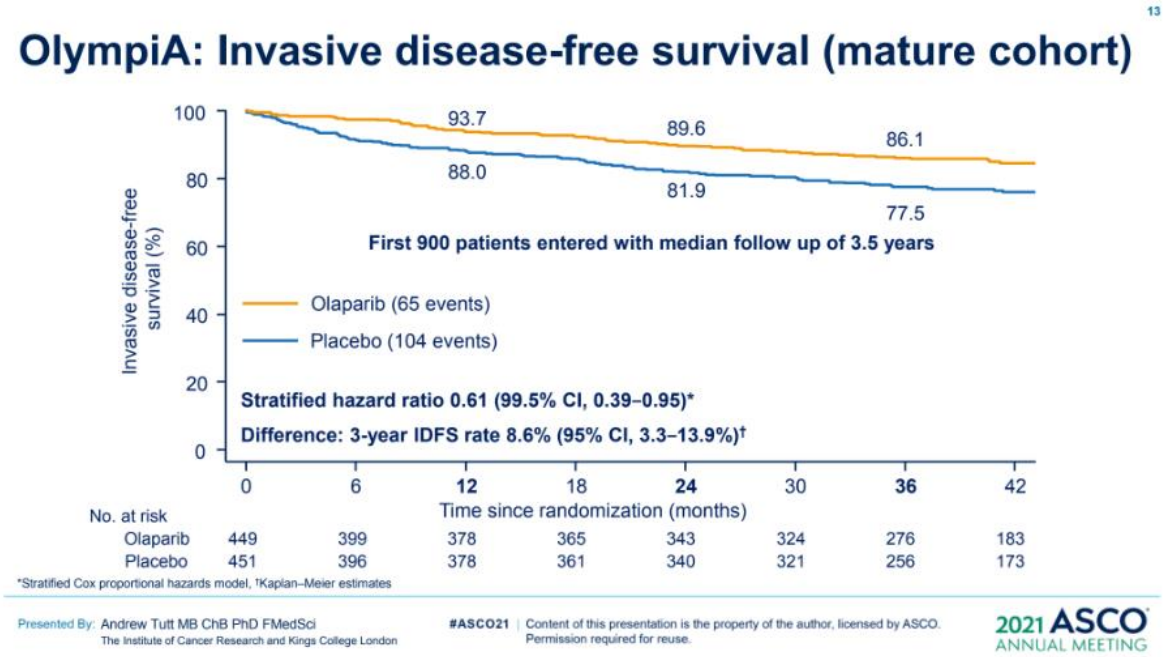

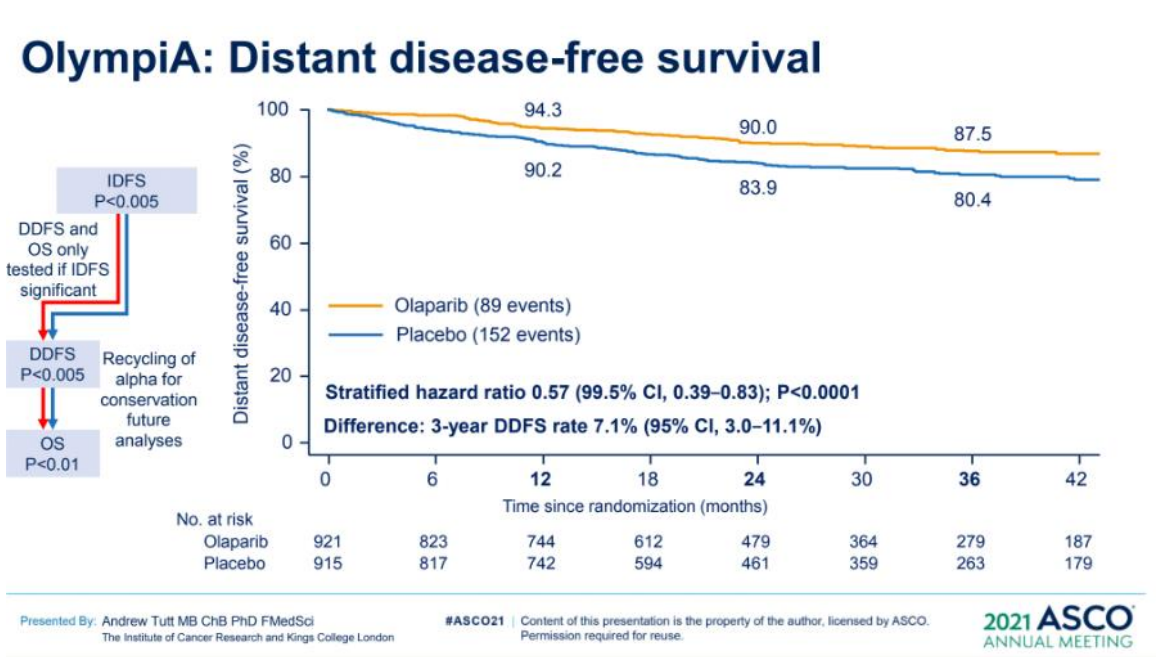

Review of current testing recommendations for patients with breast cancer (NCCN v1.2021)

- Breast cancer diagnosed with at least one of the following:
  - Diagnosed ≤ 45y
  - Diagnosed 46-50 with unknown/limited family hx or second breast cancer at any age, or ≥ 1 close relative with breast, ovarian, pancreatic, or prostate cancer
  - Diagnosed ≤ 60y with triple negative
  - Diagnosed any age with Ashkenazi Jewish ancestry, ≥ 1 close relative with breast ≤ 50y, ovarian, pancreatic, or metastatic/high risk prostate cancer
    - ≥ 3 dx of breast cancer in patient and/or close blood rels
  - Male breast cancer

Application to practice

- Be on the lookout for updates to practice guidelines – some patients who had good outcomes in Olympia and would need genetic testing would not meet current testing criteria
- Important to make available genetic counseling/testing for appropriate patients
  - Population of “appropriate patients” continues to grow
- Consider alternative service delivery models
  - Abstract 10580: 2184 unselected breast cancer survivors seen at NP-led survivorship clinic were screened to determine if adequate germline testing had been done
    - 411 were identified as testing appropriate
    - Testing offered on-site through survivorship clinic
    - 7/411 declined testing
    - 10% tested positive

Abstract 10504: Underdiagnosis of germline genetic prostate cancer: Are genetic testing guidelines an aid or an impediment?

- PROCLAIM - Multicenter trial enrolled patients with prostate cancer who had not previously had genetic testing
- Underwent germline testing for mutations in 84 genes
- 69/640 (8%) had pathogenic or likely pathogenic mutations detected
  - Mutations detected in (decreasing order): CHEK2, HOXB13, BRCA2, MITF, BRCA1, TP53, ATM, BRIP1, PALB2, PMS2, others
  - 19% of mutations were in BRCA1/2
  - Median age: 70 (range 44-90)
  - 42% of those with mutations did **not** meet current clinical criteria for testing

Review of current testing recommendations for patients with prostate cancer

- Germline genetic testing recommended for patients with prostate cancer AND:
  - High risk, very high risk, regional, or metastatic prostate cancer
  - Ashkenazi Jewish ancestry
  - Germline mutation in the family
  - Strong family history (a brother or father or multiple other family members) with prostate cancer that is not clinically localized grade 1 an <60 years or who died from prostate cancer
  - ≥ 3 cancers on same side of family, especially under age ≤ 50: Bile duct, breast, colon, endometrial, gastric, kidney, melanoma, ovarian, pancreatic, prostate (not clinically localized grade 1), small bowel, urothelial

Application to practice (similar to above)

- Similar to Olympia summary, population of “appropriate patients” continues to grow
- Genetic counseling/testing availability important in both oncology and urology
- Consider alternative service delivery models
  - Telehealth can be effective
  - Point of care – go to where patients are

Opportunity to prevent cancer – cascade testing

- Once a germline pathogenic variant (mutation) is identified in a family, family members should be offered testing for the family's variant (cascade testing)
  - Typically communication led by patient – many barriers
  - Make possible in your clinics
  - Opportunity to mitigate cancer risk

Abstract 10515: Limitations of direct-to-consumer (DTC) genetic testing for hereditary breast and ovarian cancer.

- DTC testing is available as a self-purchase and can include analysis for 3 BRCA1/2 founder mutations common in the Ashkenazi Jewish population
- Clinical grade multi-gene panel testing was performed for 348,692 high risk women and 7,636 presumed “healthy” women
  - AJ founder mutations accounted for only 30% of mutations found in healthy women
  - Even in AJ individuals, testing restricted to these 3 founder mutations would miss 10% of mutations

Application to practice

- False reassurance from DTC testing could impact health behaviors and potentially cancer screening
- Community providers should continue to raise awareness among colleagues and patients that DTC testing is not a substitute for clinical testing ordered by an HCP

Conclusions

- Population of oncology patients who could benefit from genetic counseling/testing continues to grow
  - Olympia trial showed promising results in breast cancer patients with HER2-negative disease and high risk features
  - Current prostate cancer testing guideline adherence would miss some patients with “actionable” genetic test results
- To increase access to genetic counseling/testing, alternative models of service delivery can be considered
- As patients are exposed to DTC genetic testing options, clinicians should be clear in communicating their limitations