Tumor Sequencing and Next-Generation Sequencing

Edward Tanner, MD
Division of Gynecologic Oncology
No Disclosures
Objectives

• Review the role of tumor genomics in ovarian cancer

• Discuss the potential uses of next-generation sequencing for ovarian cancer
Classifying Ovarian Cancer

Serous

Mucinous

Endometrioid
Precision Medicine

• Tailor treatments to genetic changes in each patient’s cancer

• The promise:
  – Find new/unexpected treatments
  – Avoid ineffective and toxic treatments

• A work in progress…
What can vary between tumors?

• **Germline mutations**: inherited mutations (ex. BRCA)

• **Somatic mutations**: mutations found in tumor but not in other cells

• **Functional changes**: more complex but can include epigenetic changes
Germline versus Somatic

Somatic mutations
- Occur in nongermline tissues
- Cannot be inherited

Somatic mutations
- Occur in tumor only (for example, breast)

Germline mutations
- Present in egg or sperm
- Can be inherited
- Cause cancer family syndrome

Germline mutations
- Mutation in egg or sperm
- All cells affected in offspring

Note: blood tests will *generally* not pick up somatic mutations

Adapted from the National Cancer Institute and the American Society of Clinical Oncology
Germline Testing

• Usually a blood or saliva test
• Inherited mutations
  – BRCA mutations
  – Lynch syndrome
  – Other rare conditions
• Useful for counseling about other cancers but also for some therapeutic options:
  – BRCA: PARP inhibitors
  – Lynch syndrome: immunotherapies
Somatic Mutation Testing: Next Generation Sequencing (NGS)

• Must test the tumor
  – Direct tumor biopsy
  – Tumor cells in blood stream

• How to obtain tumor:
  – Use material already available (i.e. from prior surgery)
  – Obtain a new biopsy (unclear benefit to obtaining new material rather than using old)
Somatic Mutation Testing: Next Generation Sequencing (NGS)

• Several commercial tests available
• General testing concept:
  – Assess DNA of tumors
  – Assess RNA of tumors
  – Compare to normal tissues
• Generally covered by insurance
How is this useful?

• Not useful for all patients (yet)
• Several classes of treatments:
  – BRCA-like mutations: PARP inhibitors
  – Immunogenic tumors: immunotherapies
  – Chemotherapy sensitivity: response to standard agents
  – Response to non-ovarian regimens
  – Clinical trial enrollment
BRCA-like mutations

• Somatic mutations in BRCA or other similar genes/homologous recombination deficiency (HRD)

• Treatments: PARP inhibitors
  – After primary chemotherapy (maintenance)
  – After chemotherapy for first recurrence
  – As a single agent for recurrent disease
Immunogenic tumors

• Several types:
  – Lynch genes (MLH1, MSH2, MSH6, PMS2)
  – High PD-1 expression
  – High tumor burden

• Treatments: pembrolizumab
  – Checkpoint inhibitor (more by Dr. Matei)
  – FDA approved *independent of tumor type*
Chemotherapy sensitivity

• Specific genes correlate with chemotherapy response (maybe)

• Treatments:
  – ERCC1: cisplatin/carboplatin
  – Topo I: topotecan
  – ARID1: PARP inhibitors
  – VEGF: bevacizumab
  – Hormone receptors: aromatase inhibitors

• Guide sequence of therapy, not options
Response to non-ovarian regimens (some off label uses)

- Identify genes correlating with therapy response to non-ovarian cancer specific drugs or drugs generally inactive in ovarian cancer

- **Treatments:**
  - NTRK: entrectinib (NTRK inhibitor, FDA approved)
  - ARID1A: HDAC inhibitors
  - Her-2: trastuzumab (Herceptin)

- **Other examples:** treatments for colon, lung or breast cancers
Clinical Trials

• May find mutations that qualify for a trial
  – Ovarian cancer specific trials (rare)
  – Non-disease specific trials (more common)
  – Often early phase trials

• NGS reports often list available trials
NGS: Not Perfect

• Most patients do not yet have actionable mutations

• Insurance usually covers testing but this is not guaranteed

• Must have tissue available for testing

• Speak to your oncologist about it!
THANK YOU