CONSIDERATIONS FOR THE ONCOLOGIST WHEN TREATING CANCER PATIENTS WITH GERMLINE MUTATIONS
I have no disclosures
SUMMARY

- Therapeutic potential of germline mutations
- Role of germline genetics in current cancer care
  - Predictive versus prognostic
  - Examples of impact on therapy decisions
  - Follow up post cancer diagnosis
- Finding patients with germline mutations
  - Indicators
  - Genetic testing
- New models of treatment-focused genetic assessment
THERAPEUTIC POTENTIAL OF GERMLINE MUTATIONS
Mutation is present in all body cells
- Present in every tumour cell
- Additional somatic mutations
- Favourable therapeutic index

Therapy selection simplified (potentially)
- Less genetic diversity
- Reversions/resistance mechanisms still important
THERAPEUTIC POTENTIAL OF GERMLINE MUTATIONS - MECHANISMS

- Oncogene addiction”
  - RET proto-oncogene in MEN/MTC and TKIs

- Tumour suppressor genes and “synthetic lethality”
  - BRCA gene mutations and PARP inhibitors
PREDICTIVE VERSUS PROGNOSTIC IMPLICATIONS OF GERMLINE MUTATION STATUS
PROGNOSTIC IMPLICATIONS

- The presence of a germline mutation affects overall survival independent of therapy
  - BRCA and ovarian cancer survival
  - Mismatch repair (MMR) mutations and colorectal cancer survival

- Should germline mutation status be a stratification factor in clinical trials?
  - Ovarian
  - Colorectal
The presence of a germline mutation affects overall survival independent of therapy
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Should germline mutation status be a stratification factor in clinical trials?
- Ovarian
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**Association Between BRCA1 and BRCA2 Mutations and Survival in Women With Invasive Epithelial Ovarian Cancer**

*JAMA. 2012;307(4):382-390*

**Context.** Approximately 10% of women with invasive epithelial ovarian cancer (EOC) carry deleterious germline mutations in BRCA1 or BRCA2. A recent article suggested...
The presence of a germline mutation affects overall survival independent of therapy

- BRCA and ovarian cancer survival
- Mismatch repair (MMR) mutations and colorectal cancer survival

Should germline mutation status be a stratification factor in clinical trials?

- Ovarian
- Colorectal

**DNA Mismatch Repair Status and Colon Cancer Recurrence and Survival in Clinical Trials of 5-Fluorouracil-Based Adjuvant Therapy**

Frank A. Sinicrope, Nathan R. Foster, Stephen N. Thibodeau, Silvia Marsoni, Genevieve Monges, Roberto Labianca, Greg Yothers, Carmen Allegra, Malcolm J. Moore, Steven Gallinger, Daniel J. Sargent

*J Natl Cancer Inst* 2011;103:863–875

**Prognostic Impact of Deficient DNA Mismatch Repair in Patients With Stage III Colon Cancer From a Randomized Trial of FOLFOX-Based Adjuvant Chemotherapy**

PREDICTIVE IMPLICATIONS

- Likelihood of response to therapy
  - BRCA (+other homologous-repair pathway gene mutations?)
    - PARP inhibitors
    - Other DNA-damaging agents
    - Response to taxanes?

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**Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and advanced breast cancer: a proof-of-concept trial**

Andrew Tutt, Mark Robson, Judy E Garber, Susan M Domchek, M William Audeh, Jeffrey N Weitzel, Michael Friedlander, Bonu Arun, Niklas Loman, Rita K Schmutzler, Andrew Wardley, Gillian Mitchell, Helena Earl, Mark Wickens, James Carmichael

**Summary**

Olaparib, a novel, orally active poly(ADP-ribose) polymerase (PARP) inhibitor, induced synthetic lethality in BRCA-deficient cells. A phase IIa trial led to an initial signal of efficacy in BRCA1-deficient ovarian cancer patients.
PREDICTIVE IMPLICATIONS

- Likelihood of response to therapy
  - BRCA (+other homologous repair pathway gene mutations?)
  - PARP inhibitors
  - Other DNA-damaging agents
  - Response to taxanes
  - MMR mutations
    - 5FU-based therapy
    - Oxaliplatin/irinotecan

Defective Mismatch Repair As a Predictive Marker for Lack of Efficacy of Fluorouracil-Based Adjuvant Therapy in Colon Cancer


Cancer Res; 18(23); 6531–41

Mutation Profiling and Microsatellite Instability in Stage II and III Colon Cancer: An Assessment of Their Prognostic and Oxaliplatin Predictive Value

CURRENT EXAMPLES
WHAT TREATMENT MODALITIES ARE AFFECTED?

- Extent of surgery
- Role of radiotherapy
- Choice of chemotherapy
Breast cancer

  - Breast conservation versus bilateral mastectomy?
  - Avoiding ionising radiation? *EJC* 2013 Sep;49(14):2979-85

Colorectal cancer

  - Limited versus extended resection
  - Rectal sparing or not?
  - +/- hysterectomy (+/- bilateral salpingo-oophorectomy)
ROLE OF RADIOTHERAPY

- High risk of radiation-induced malignancies
  - TP53 = Li Fraumeni syndrome
  - PTCH = Gorlin syndrome
  - DNA-repair syndromes??????

Clin Oncol 2005 Dec;17(8):650-4
CHOICE OF CHEMOTHERAPY

- Modality with most rapidly increasing range of choices impacted by germline mutation status
  - Targeted agents

- BRCA/double strand DNA repair defects
  - PARP inhibitors in breast/ovarian cancer

- MMR (Lynch syndrome)
  - 5FU-based therapy
  - Oxaliplatin/irinotecan?  JCO 2009 10;27(11):1814-21

- RET (MEN2/medullary thyroid cancers)
  - Kinase inhibitors  JCO 2013 31(29):3639-46

- PTCH (Gorlin syndrome)
  - Smoothened inhibitors
Modality with most rapidly increasing range of choices impacted by germline mutation status

- Targeted agents
  - BRCA/double strand DNA repair defects
    - Platinum in breast cancer therapy
    - PARP inhibitors in breast/ovarian cancer
  - MMR (Lynch syndrome)
    - 5FU-based therapy
    - Oxaliplatin/irinotecan
    - Methotrexate
  - RET (MEN2/medullary thyroid cancers)
    - Kinase inhibitors

- PTCH (Gorlin syndrome)
  - Smoothened inhibitors
Screening and prevention strategies

- More intensive screening
  - Colonoscopy and upper GI endoscopy (Lynch Syndrome)
  - Breast MRI screening (breast cancer predisposition syndromes)
  - Whole-body MRI for multi-organ cancer syndromes?

- Risk-reducing medications for breast cancer (even if ER negative cancer?)
  - SERM
  - Aromatase inhibitor
  - Risk-reducing medication for CRC
    - Aspirin

Life-long follow up required
FINDING PATIENTS WITH A GERMLINE CANCER PREDISPOSITION
INDICATORS OF A CANCER PREDISPOSITION

- Pre-existing knowledge of a mutation in the family
- Personal features
  - Age of onset
  - Type of cancer
  - Tumour location and/or pathology
- Family history
  - A strong indicator
  - Absence of a family history is not reassuring
- Active tumour screening
  - IHC for MMR protein expression/Microsatellite instability
  - IHC for SDHB protein expression (phaeochromocytomas)
Local circumstances will guide testing environment
  - Direct testing by oncology specialist
  - Testing through local genetics services

Important to have a timely assessment
  - Counselling
  - Testing

Important to have an accurate interpretation of family history and genetic test result
NEW MODELS OF TREATMENT-FOCUSED GENETIC ASSESSMENT
MODELS

- Oncology clinic-based germline genetic testing
  - Protocols developed with local genetics services to ensure informed consent, interpretation, ongoing management of patients and their families

- +/- panel testing

- Tumour sequencing
Germline gene mutations associated with cancer predisposition syndromes can impact
- On cancer treatment selection
- Cancer treatment outcomes

The indications for the integration of germline gene mutations into cancer treatment are increasing rapidly

Germline genetic testing will become a more essential component of management in many cancer presentations

Germline gene mutations will be discovered as part of tumour sequencing for therapeutic purposes