CONSIDERATIONS FOR THE ONCOLOGIST WHEN TREATING CANCER PATIENTS WITH GERMLINE MUTATIONS

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DISCLOSURES

- 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

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- 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

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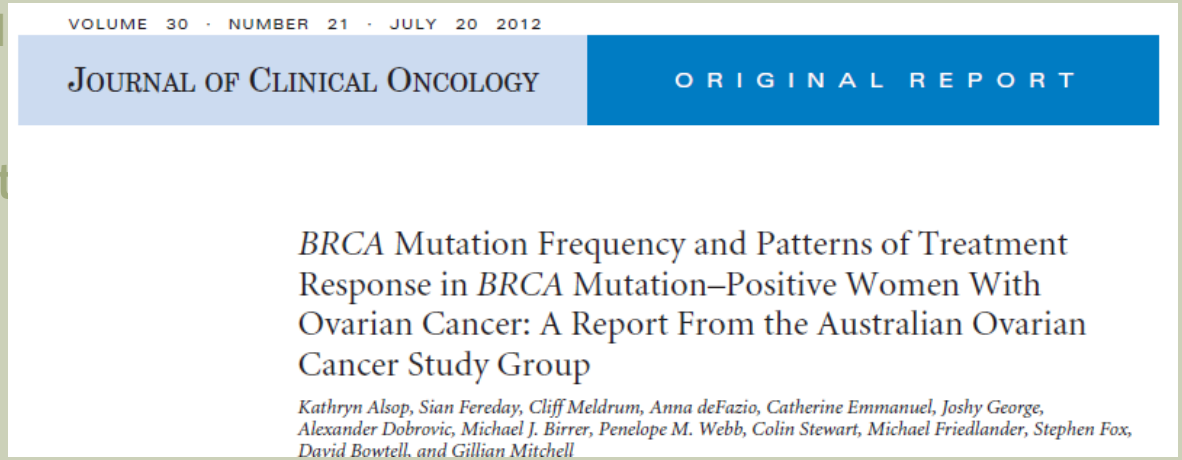

VOLUME 30 · NUMBER 21 · JULY 20 2012

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

BRCA Mutation Frequency and Patterns of Treatment Response in *BRCA* Mutation–Positive Women With Ovarian Cancer: A Report From the Australian Ovarian Cancer Study Group

Kathryn Alsop, Sian Fereday, Cliff Meldrum, Anna deFazio, Catherine Emmanuel, Joshy George, Alexander Dobrovic, Michael J. Birrer, Penelope M. Webb, Colin Stewart, Michael Friedlander, Stephen Fox, David Bowtell, and Gillian Mitchell

Association Between *BRCA1* and *BRCA2* Mutations and Survival in Women With Invasive Epithelial Ovarian Cancer

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

Kelly L. Bolton, PhD, Georgia Chenevix-Trench, PhD, Cindy Goh, BA, Siegal Sadetzki,

Context Approximately 10% of women with invasive epithelial ovarian cancer (EOC)

PROGNOSTIC IMPLICATIONS

- The presence of a germline mutation affects overall survival independent of therapy
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  clinical tr
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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. Sargen

J Natl Cancer Inst 2011;103:863–875

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JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

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

Frank A. Sinicrope, Michelle R. Mahoney, Thomas C. Smyrk, Stephen N. Thibodeau, Robert S. Warren, Monica M. Bertagnolli, Garth D. Nelson, Richard M. Goldberg, Daniel J. Sargent, and Steven R. Alberts

PREDICTIVE IMPLICATIONS

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

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, Banu Arun, Niklas Loman, Rita K Schmutzler, Andrew Wardley, Gillian Mitchell, Helena Earl, Mark Wickens, James Carmichael

Summary

Background Olaparib, a novel, orally active poly(ADP-ribose) polymerase (PARP) inhibitor, induced synthetic

Lancet 2010; 376: 235–44

PREDICTIVE IMPLICATIONS

- Likelihood of re
  - BRCA (+other h
    - PARP inhibito
    - Other DNA-da
    - Response to t
  - MMR mutations
    - 5FU-based therapy
    - Oxaliplatin/irinotecan

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

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

Daniel J. Sargent, Silvia Marsoni, Genevieve Monges, Stephen N. Thibodeau, Roberto Labianca, Stanley R. Hamilton, Amy J. French, Brian Kabat, Nathan R. Foster, Valter Torri, Christine Ribic, Axel Grothey, Malcolm Moore, Alberto Zaniboni, Jean-Francois Seitz, Frank Sinicrope, and Steven Gallinger

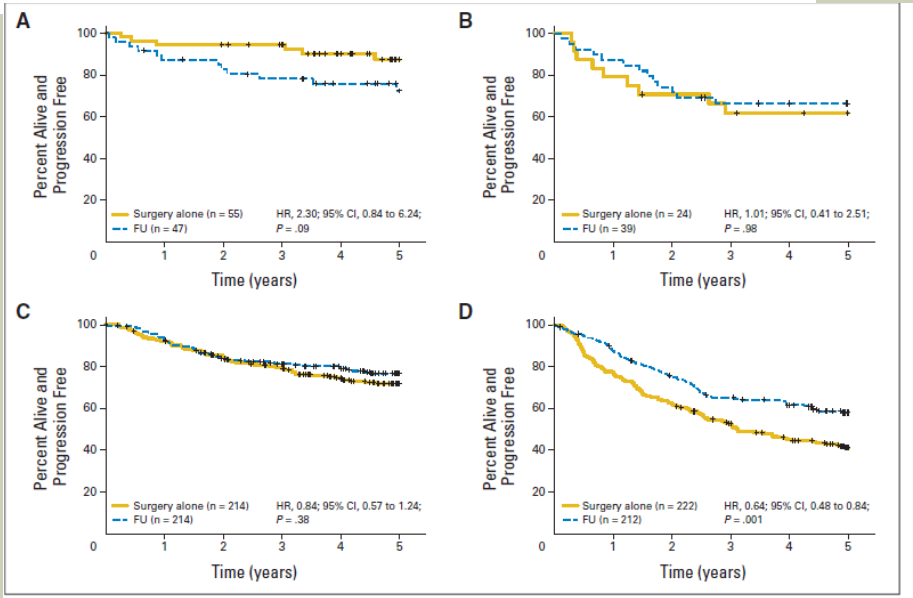


Fig 2. (A) Disease-free survival (DFS) in patients with stage II disease and defective DNA mismatch repair (dMMR) by treatment status. (B) DFS in patients with stage III disease and dMMR by treatment status. (C) DFS in patients with stage II disease and proficient MMR (pMMR) by treatment status. (D) DFS in patients with stage III disease and pMMR by treatment status. HR, hazard ratio; FU, fluorouracil.

Cancer Res; 18(23); 6531–41

Predictive Biomarkers and Personalized Medicine

Clinical Cancer Research

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

Patrick G. Gavin[1], Linda H. Colangelo[1,2,3], Debora Fumagalli[1], Noriko Tanaka[1,2,3], Matthew Y. Remillard[1], Greg Yothers[1,2,3], Chungyeul Kim[1], Yusuke Taniyama[1], Seung Il Kim[1], Hyun Joo Choi[1], Nicole L. Blackmon[1], Corey Lipchik[1], Nicholas J. Petrelli[1,5], Michael J. O'Connell[1], Norman Wolmark[1,4], Soonmyung Paik[1], and Kay L. Pogue-Geile[1]

CURRENT EXAMPLES

WHAT TREATMENT MODALITIES ARE AFFECTED?

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

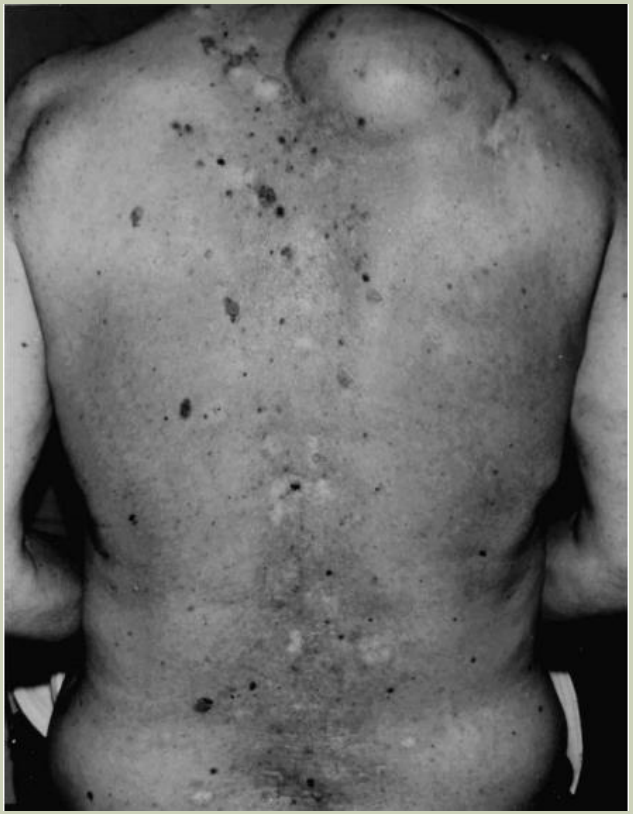
EXTENT OF SURGERY

- Breast cancer
  - BRCA/TP53/PTEN/CDH1/STK11/PALB2?/CHK2? = High risk of second primary breast cancers JCO 2009 27(35):5887-92
    - Breast conservation versus bilateral mastectomy?
    - Avoiding ionising radiation? EJC 2013 Sep;49(14):2979-85

- Colorectal cancer
  - Lynch syndrome (MMR gene mutations) = high risk of second primary CRC and gynaecological cancers JNCI 2012 104(18):1363-72; Gut. 2011 60 (7):950-7
    - 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
  - Platinum in breast cancer therapy — Br Ca Res Treat. 2014 147(2):401-5
  - PARP inhibitors in breast/ovarian cancer
- MMR (Lynch syndrome)
  - 5FU-based therapy
  - Oxaliplatin/irinotecan? — JCO 2009 10;27(11):1814-21
  - Methotrexate? — EMBO Mol Med. 2009 Sep;1(6-7):323-37
- RET (MEN2/medullary thyroid cancers)
  - Kinase inhibitors — JCO 2013 31(29):3639-46
- PTCH (Gorlin syndrome)
  - Smoothened inhibitors

CHOICE OF CHEMOTHERAPY

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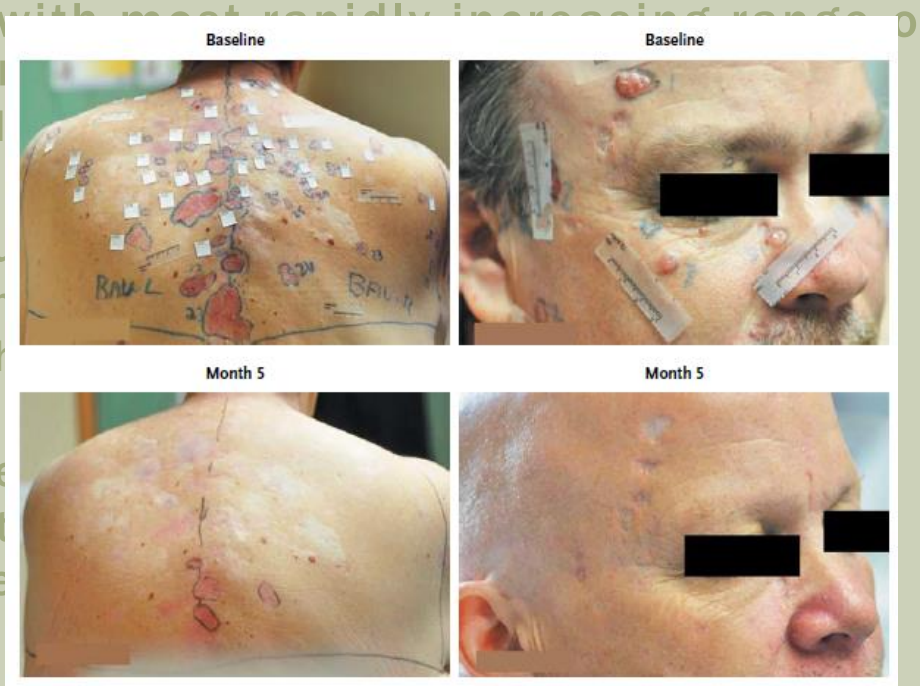
- PTCH (Gorlin syndrome)
  - Smoothened inhibitors
  - Tang et al N Engl J Med 2012; 366:2180-2188



POST CANCER FOLLOW UP

- 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)

GENETIC TESTING

- 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-FOCUSSED 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

CONCLUSION

- 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