germline mutation detected in men with breast cancer and this mutation also confers increased risks for prostate cancer.

The International Male Breast Cancer Program also includes a prospective study of new male breast cancer diagnoses with tumour collection, as well as prospective clinical studies testing the efficacy of breast cancer treatments in men. In the future such research will hopefully provide greater insights into the pathobiology and prognosis of male breast cancer, and enable evidence-based optimal management.

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References

1. Giordano S, Cohen D, Buzdar A et al. Breast carcinoma in men: a population-based study. Cancer 2004; 101(1): 51–57.
2. Cardoso F, Bartlett JMS, Slaets L et al. Characterization of male breast cancer: results of the EORTC 10085/TBCRC/BIG/NABCG International Male Breast Cancer Program. Ann Oncol 2018; 29(2): 405–417.
3. Vermeulen MA, Slaets L, Cardoso F et al. Pathological characterisation of male breast cancer: results of the EORTC 10085/TBCRC/BIG/NNABCG International Male Breast Cancer Program. Eur J Cancer 2017; 82: 219–227.
4. Doebar SC, Slaets L, Cardoso F et al. Male breast cancer precursor lesions: analysis of the EORTC 10085/TBCRC/BIG/NABCG International Male Breast Cancer Program. Mod Pathol 2017; 30(4): 509–518.
5. Prat A, Cheang MC, Martin M et al. Prognostic significance of progesterone receptor-positive tumour cells within IHC defined luminal A breast cancer. J Clin Oncol 2013; 31: 203–209.
6. Piscuoglio S, Ng CKY, Murray MP et al. The genomic landscape of male breast cancers. Clin Cancer Res 2016; 22(16): 15.
7. Zagouri F, Sergentanis TN, Chrysikos D et al. Fulvestrant and male breast cancer: a pooled analysis. Breast Cancer Res Treat 2015; 149(1): 269–275.
8. Zagouri F, Sergentanis TN, Azim HA et al. Aromatase inhibitors in male breast cancer: a pooled analysis. Breast Cancer Res Treat 2015; 151(1): 141–147.
9. Kim ES, Bruinooge SS, Roberts S, et al. Broadening eligibility criteria to make clinical trials more representative: American Society of Clinical Oncology and Friends of Cancer Research joint research statement. J Clin Oncol 2017; 35: 3737–3744.
10. Turner C, Ro J, Andre F et al. Palbociclib in hormone-receptor-positive advanced breast cancer. N Engl J Med 2015; 373(3): 209–219.
11. Sorscher S. A first case of male breast cancer responding to combined aromatase inhibitor/palbociclib therapy. Int J Cancer Clin Res 2016; 3(5): 069.
12. Von Minckwitz G, Procter M, de Azambuja E et al. Adjuvant pertuzumab and trastuzumab in early HER2-positive breast cancer. N Engl J Med 2017; 377(2): 122–131.
13. Tai Y, Domchek S, Parmigiani G et al. Breast cancer risk among male BRCA1 and BRCA2 mutation carriers. J Natl Cancer Inst 2007; 99: 1811–1814.

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Pharmacogenomics: time to rethink its role in precision medicine

The complex genetic landscape of human cancer is evident not only across cancers from different primary sites, but also amongst cancers of the same histopathologic subtype. Understanding the contribution of this genetic landscape to relevant clinical end points such as overall survival (OS), treatment response, and toxicity has helped facilitate the evolution and application of precision clinical oncology [1, 2]. Over the past several years, specific challenges posed by genetic heterogeneity have led to the implementation of novel biomarker-based clinical trial designs for drug development, which have led to improved survival for patients with a wide variety of tumor types [3]. However, whereas many of these successful biomarker-based clinical trials have utilized somatic mutation profiling, relatively fewer studies have harnessed the area of pharmacogenomics and germline variation.

For colorectal cancer (CRC), the role of germline variation in the efficacy and toxicity of cytotoxic chemotherapy has been the subject of widespread investigation [4]. Dihydropyrimidine dehydrogenase (*DPYD*) gene variation is a well-established example, whereby deleterious single-nucleotide polymorphisms in *DPYD* have been associated with severe toxicity to 5-fluorouracil (5-FU) therapy [5, 6]. However, despite multiple lines of evidence that specific *DPYD* variants can reliably predict 5-FU toxicity, a number of issues currently limit pre-treatment *DPYD* testing from standard clinical practice, namely: regional differences in population allele frequency, technical variation in genotyping methods, and a paucity of large-scale randomized studies [7]. Germline variation in UDP-glucuronosyltransferase 1A1 (*UGT1A1*) presents a similar example, in which the *UGT1A1*28* polymorphism is associated with an increased risk of irinotecan toxicity due to decreased drug metabolism [8–10]. As in the case for *DPYD*, widespread testing for *UGT1A1* polymorphisms in CRC patients remains controversial. It is noteworthy that neither the National Comprehensive Cancer Network (NCCN) [11] nor European Society of Medical Oncology (ESMO) [12] guidelines currently recommend routine clinical testing of *DPYD* and *UGT1A1* polymorphisms. This not only reflects the practical challenges of incorporating germline variability into therapeutic decision-making, but also signifies an opportunity to discover novel germline biomarkers through innovative approaches.

In this issue of *Annals of Oncology*, Abad and Martinez-Balibrea et al. describe the results of a rigorous multi-center study that examined the feasibility and clinical utility of using germline DNA biomarkers to select front-line chemotherapy for patients with metastatic CRC (mCRC) [13]. Using a randomized, phase II, open-label design, a total of 195 Spain-based patients with

mCRC were randomized to receive either standard front-line chemotherapy with XELOX plus bevacizumab (control group, $n = 61$) or a genotype-driven regimen (experimental group, $n = 130$) selected based upon germline variants in thymidylate synthetase (*TYMS*, 1494del6bp) and excision repair 1, endonuclease non-catalytic subunit (*ERCC1*, c.354T>C). The genotype-driven regimens included XELOX plus bevacizumab, XELIRI plus bevacizumab, FUOX plus bevacizumab, and FUIRI plus bevacizumab. With respect to the efficacy of this approach, no significant difference in progression-free survival (PFS) was observed between the control and experimental group (9.4 versus 10.1 months)—and thus the primary end point of the study was not met. However, modest significant improvements were observed in response rate (control 33% versus experimental 48%) and R0 metastatic resection rate (44% versus 86%). Notably, toxicities also varied between the treatment groups, with significantly lower rates of neuropathy but higher rates of grade 3 diarrhea in the experimental group.

Thymidylate synthetase carries out a critical step in the generation and maintenance of intracellular deoxythymidylate, which in turn is necessary for DNA maintenance. As the primary intracellular target for fluoropyrimidines (such as 5-FU), it has been hypothesized that *TYMS* gene expression and enzymatic activity are important mediators of treatment efficacy and/or toxicity with fluoropyrimidines-based chemotherapy regimens [14–17]. The *TYMS* 1494del6bp variant has a global allele frequency of 49% (based on 1000 Genomes project data) and is thought to confer decreased message RNA stability by disruption of 3' untranslated region [18, 19]. Similarly, *ERCC1* is an important component of the nucleotide excision repair pathway, which recognizes DNA adducts formed by platinum-containing agents (e.g. oxaliplatin) and thus is hypothesized to modulate their potency [20–23]. *ERCC1* c.354T>C is a common variant (global allele frequency 33%) that is associated with decrease mRNA expression in vitro models [24].

For CRC, the efficacies of 5-FU- and/or oxaliplatin-based treatment regimens have been well-established across (neo)adjuvant and metastatic disease settings. Thus, understanding both extrinsic and intrinsic factors that regulate *TYMS* and *ERCC1* activity is particularly relevant for patients with mCRC. The work by Abad and Martinez-Balibrea et al. contributes additional data on the relative value of *TYMS* 1494del6bp and *ERCC1* c.354T>C as clinically useful biomarkers in the treatment of mCRC patients with standard cytotoxic chemotherapy. Yet, as the primary end point of their study was not met, it would not be reasonable to launch future pharmacogenomic biomarker-driven trials involving solely the determination of *TYMS* and *ERCC1* to guide therapy compared with current standards of practice with the goal to improve OS.

Broadly speaking, Abad and Martinez-Balibrea et al. demonstrate that it is technically and logistically feasible to implement a germline biomarker-driven strategy in CRC. At least two features of their study design were key to its successful implementation: (i) centralized genotyping pipelines and (ii) careful attention to regional variation in genetic substructure. However, their results again highlight important challenges and limitations facing the pharmacogenomics community. The complex interplay between clinical covariates, germline variations, and somatic alterations is likely to be a major determinant of whether a germline biomarker-driven strategy translates into improved PFS or OS. To help advance this strategy further, it is time to rethink the role of pharmacogenomics within the big picture of predictive biomarkers that are available in the space of CRC oncology. In fact, it would be helpful to integrate both worlds: germline and somatic mutation profiling into future large-scale, prospective clinical investigations. This could enable exploration of a complex combinatorial space and broaden applicability—principles that are important not only for cytotoxic therapy, but also the next generation of targeted and biological therapies.

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References

1. Biankin AV, Piantadosi S, Hollingsworth SJ. Patient-centric trials for therapeutic development in precision oncology. Nature 2015; 526(7573): 361.
2. Sleijfer S, Bogaerts J, Siu LL. Designing transformative clinical trials in the cancer genome era. JCO 2013; 31(15): 1834–1841.
3. Schwaederle M, Zhao M, Lee JJ et al. Impact of precision medicine in diverse cancers: a meta-analysis of phase II clinical trials. JCO 2015; 33(32): 3817–3825.
4. Panczyk M. Pharmacogenetics research on chemotherapy resistance in colorectal cancer over the last 20 years. WJG 2014; 20(29): 9775–9827.
5. Mattison LK, Soong R, Diasio RB. Implications of dihydropyrimidine dehydrogenase on 5-fluorouracil pharmacogenetics and pharmacogenomics. Pharmacogenomics 2002; 3(4): 485–492.
6. Meulendijks D, Henricks LM, Sonke GS et al. Clinical relevance of DPYD variants c.1679T>G, c.1236G>A/HapB3, and c.1601G>A as predictors of severe fluoropyrimidine-associated toxicity: a systematic review and meta-analysis of individual patient data. Lancet Oncol 2015; 16(16): 1639–1650.
7. Ciccolini J. DPD deficiency in patients treated with fluorouracil. Lancet Oncol 2015; 16(16): 1574–1576.
8. O'Dwyer PJ, Catalano RB. Uridine diphosphate glucuronosyltransferase (UGT) 1A1 and irinotecan: practical pharmacogenomics arrives in cancer therapy. J Clin Oncol 2006; 24: 4534–4538.
9. Innocenti F, Undevia SD, Iyer L et al. Genetic variants in the UDP-glucuronosyltransferase 1A1 gene predict the risk of severe neutropenia of irinotecan. J Clin Oncol 2004; 22(8): 1382–1388.
10. Toffoli G, Cecchin E, Gasparini G et al. Genotype-driven phase I study of irinotecan administered in combination with fluorouracil/leucovorin in patients with metastatic colorectal cancer. JCO 2010; 28(5): 866–871.
11. National Comprehensive Cancer Network. Colon Cancer (Version 3.2017). https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf (27 November 2017, date last accessed).

12. Van Cutsem E, Cervantes A, Adam R et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. Ann Oncol 2016; 27(8): 1386–1422.
13. Abad A, Martínez-Balibrea E, Viéitez JM et al. Genotype-based selection of treatment for patients with advanced colorectal cancer (SETICC): a pharmacogenetic-based randomized phase II trial. Ann Oncol 2018; 29(2): 439–444.
14. Johnston PG, Fisher ER, Rockette HE et al. The role of thymidylate synthase expression in prognosis and outcome of adjuvant chemotherapy in patients with rectal cancer. JCO 1994; 12(12): 2640–2647.
15. Johnston PG, Lenz H-J, Leichman CG et al. Thymidylate synthase gene and protein expression correlate and are associated with response to 5-fluorouracil in human colorectal and gastric tumors. Cancer Res 1995; 55: 1407–1412.
16. Lenz HJ, Danenberg KD, Leichman CG et al. p53 and thymidylate synthase expression in untreated stage II colon cancer: associations with recurrence, survival, and site. Clin Cancer Res 1998; 4: 1227–1234.
17. Tan BR, Thomas F, Myerson RJ et al. Thymidylate synthase genotype-directed neoadjuvant chemoradiation for patients with rectal adenocarcinoma. JCO 2011; 29(7): 875–883.
18. Lurje G, Manegold PC, Ning Y et al. *Thymidylate synthase* gene variations: predictive and prognostic markers. Mol Cancer Ther 2009; 8: 1000–1007.
19. The Genomes Project C. A global reference for human genetic variation. Nature 2015; 526: 68.
20. Martinez-Balibrea E, Abad A, Aranda E et al. Pharmacogenetic approach for capecitabine or 5-fluorouracil selection to be combined with oxaliplatin as first-line chemotherapy in advanced colorectal cancer. Eur J Cancer 2008; 44(9): 1229–1237.
21. Viguier J, Boige V, Miquel C et al. *ERCC1* Codon 118 polymorphism is a predictive factor for the tumor response to oxaliplatin/5-fluorouracil combination chemotherapy in patients with advanced colorectal cancer. Clin Cancer Res 2005; 11: 6212–6217.
22. de las Peñas R, Sanchez-Ronco M, Alberola V et al. Polymorphisms in DNA repair genes modulate survival in cisplatin/gemcitabine-treated non-small-cell lung cancer patients. Ann Oncol 2006; 17(4): 668–675.
23. Tan L-M, Qiu C-F, Zhu T et al. Genetic polymorphisms and platinum-based chemotherapy treatment outcomes in patients with non-small cell lung cancer: a genetic epidemiology study based meta-analysis. Sci Rep 2017; 7(1): 5593.
24. Yu JJ, Lee KB, Mu C et al. Comparison of two human ovarian carcinoma cell lines (A2780/CP70 and MCAS) that are equally resistant to platinum, but differ at codon 118 of the ERCC1 gene. Int J Oncol 2000; 16: 555–560.

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New antiemetics: facing the current challenge

Revolution starts with evolution. Progress regarding emesis has been highlighted by the American Society of Clinical Oncology Committee (https://www.asco.org/about-asco/press-center/news-releases/asco-50th-anniversary-poll-names-top-5-advances-past-50-years) as one of the five leading advances in cancer during the past 50 years. A new generation of antiemetics is approved by the FDA every 10 years leading to a significant enhancement of a no emesis response rate for patients undergoing chemotherapy. We must remember that 100% of cancer-treated patients were impacted by emesis in the seventies, whereas today, 'only' 10%–20% of patients are affected [1, 2]. Before the development of setrons (5HT3 receptor antagonists) there was a daily fight by the patient against vomiting. The NK1 inhibitor's development has radically altered the face of the emesis battle and we can now effectively assess nausea and individual risk factors [3–5].

Two new antiemetics (NK1 inhibitors) have been recently approved by the FDA:

- Rolapitant which has a very long half-life (180 h) that may cover the entire delayed phase up to 7 days [6].
- Netupitant with a long half-life (96 h), combined with palonosetron, should be reduced to a single capsule 1 h before starting chemotherapy [7–9].

Both have a galenic oral route, leading to a reduction in the out-patient stay and nurse's care involvement.

In their non-inferiority trial, Li et al., has compared a fixed combination of netupitant and palonosetron (NEPA) combined with steroids, versus an aprepitant regimen combined with steroids and granisetron [10], in order to assess the efficacy of a new NK1 inhibitor when compared with the previous antiemetic reference. The results highlighted in their article conclude in favour of the non-inferiority of NEPA.

This is the first time, to our knowledge, that a new NK1 inhibitor generation has been compared with the old-fashioned prophylaxis. In previous registration studies, NEPA has been compared with an aprepitant–ondansetron regimen, but this was in a non-pre-planned analysis [8, 9]. All the previously reported studies only compared the new NK1 inhibitors with the association of steroids and setrons. In fact, this association was the control arm of the aprepitant pivotal studies [11].

The response rate levels reached by an aprepitant combined with a standard combination, in some trials have led a 100% protection of breast cancer patients treated with an AC regimen [12].

Some comments should be addressed by the authors:

- Why conduct a non-inferiority trial?
- Statistical efficacy as regards nausea.
- Patient's characteristics.
- Cost.

Moreover, we must keep in mind that modern medicine likes comparisons and the use of evidence based data. There are very few topics in oncology that have a treatment response rate that can reach 100%.

An aprepitant NK1 inhibitor has been available for some time in the cisplatin and Anthracycline–cyclophosphamide (AC) antiemetic prophylaxis [13]. All the recently reported guidelines, published by the various oncological societies, have included all NK1-inhibitors in the prophylaxis of cisplatin, AC regimen and carboplatin [14–16]. With the article by Zhang et al., and their results, the non-inferiority trial opens the door to new perspectives. The challenges we will have to assume with the new antiemetics, in the near future are: nausea assessment and prevention, improvement and individual adaptation of prophylaxis related to individual risk factors, specificities of acute, delayed but also