Pharmacogenomics in cancer supportive care: key issues and future directions

Jai N. Patel¹ · Ian Olver² · Fred Ashbury^{3,4,5}

Received: 23 June 2021 / Accepted: 19 July 2021 / Published online: 1 August 2021
© The Author(s), under exclusive licence to Springer-Verlag GmbH Germany, part of Springer Nature 2021

Introduction

The complexity of cancer care has changed dramatically in the past decade. Advances in genomic science and proteomics have resulted in approvals of companion diagnostics, next-generation sequencing (NGS) platforms, and novel immunotherapies and targeted therapies, which offer more precise treatments in contrast to the “one-size-fits-all” chemotherapy model. These novel agents have toxicities that require different management strategies [1]. Moreover, pharmacogenomics (PGx) research shows that a better understanding of how cancer drugs and supportive agents are metabolized by patients is essential to inform clinical decision-making. We are better able to determine which patients may be at risk for side effects or drug failure based on metabolism status in order to select treatment options and/or dosages that are precise to and therefore optimal for patients [2]. Finally, there has been tremendous work developing guidelines for diagnostics, treatment, supportive care, post-treatment rehabilitation and survivorship, and palliative and end-of-life care. Therefore, it is understandable that cancer patients, busy oncology care teams, and health systems are dealing together with greater complexity, for which clearer and accessible direction is needed to support clinical decisions.

In this editorial, we focus on the clinical challenges and opportunities for effective supportive care, resulting from recent advances in PGx. The authors draw on current literature and their clinical experiences to delineate these challenges and opportunities and suggest future directions to facilitate application at point-of-care.

Clinical problem

Precision drug dosing is important for both anticancer and supportive care drugs because of interindividual variability in drug exposure [3]. Accidental overdosing in poor metabolizers (or ultrarapid metabolizers receiving a pro-drug) may result in unnecessary side effects before doses are subsequently adjusted based on tolerability [4]. For example, patients with dihydropyrimidine dehydrogenase deficiency have a significantly higher risk of developing fluoropyrimidine-related toxicities, which in rare circumstances can be fatal [5]. It is also particularly problematic for supportive care medications which are employed to prevent or treat the side effects of chemotherapy if they add significant side effects themselves. Even the gut microbiota may impact toxicity to novel immune checkpoint inhibitors [6], further complicating their use in practice.

However, underdosing will result in lack of efficacy, which may not be apparent with anticancer treatment until the next tumor measurement. Underdosing of supportive care drugs, which renders them ineffective, may result in dose reduction of the anticancer treatment to reduce its toxicity. For supportive care agents where drug exposure is related to efficacy and toxicity, therapeutic drug monitoring may address exposure variability. PGx is one component of individual variation in the required dosing but has not been routinely used to individualize drug selection or dosing because of limited robust clinical trials, barriers to accessing results in real-time at the point of care, lack of education/awareness on how to apply the results in practice, and cost [7].

✉ Jai N. Patel
jai.patel@atriumhealth.org

¹ Department of Cancer Pharmacology and Pharmacogenomics, Levine Cancer Institute, Atrium Health, 1021 Morehead Medical Drive, Rm 20161, NC, Charlotte, USA

² Department of Psychology, University of Adelaide, South Australia, Australia

³ Department of Oncology, University of Calgary, Alberta, Canada

⁴ Dalla Lana School of Public Health, University of Toronto, Toronto, ON, Canada

⁵ VieCure, Denver, CO, USA

Failure to undertake PGx testing when appropriate can result in poorer outcomes because of incorrect dosing and/or drug selection [2]. Incorrect dosing can result in increased emergency department visits due to toxicities and treatment delays, thereby deleteriously affecting outcomes [8], reduced patient satisfaction with care [2], and provider disenchantment with treatment options [9].

Dose-exposure response relationship

Drug exposure–response relationship is critical for establishing dosages used in early phase clinical trials [10]. The general hypothesis is that a higher dose results in higher exposure (measured by area under the concentration–time [AUC] curve), which leads to better response and/or increased toxicity risk. Data with certain drugs, such as monoclonal antibodies and those eliciting immune responses, have shown this is not always true [11]. For example, the dose–response or exposure–response curve may plateau at maximum target receptor occupancy, in which case higher doses may result in increased off-target effects and increased toxicity risk without added benefit.

Pharmacokinetic-guided dosing has been explored for certain chemotherapies based on the exposure–response profile and therapeutic index. One well-known example is busulfan, an alkylating agent commonly used as part of conditioning regimens for hematopoietic cell transplantation. Busulfan exhibits first-order kinetics, and its AUC has been correlated with drug-related toxicities, primarily veno-occlusive disease, and transplant relapse [12]. As a result, pharmacokinetic-guided dosing targeting prespecified AUCs or AUC ranges has become widely adopted across transplant centers, which has resulted in increased tolerability and improved transplant outcomes. However, this is the exception, and pharmacokinetic-dosing is not universal across narrow therapeutic cancer drugs.

PGx can alter drug pharmacokinetics, including metabolism, clearance, and AUC [13]. In an ideal scenario, PGx testing would be performed to preemptively assist with drug or dose selection, followed by therapeutic drug monitoring to target prespecified therapeutic concentrations or AUCs. The examples below discuss how PGx variation may impact the dose-exposure relationship for commonly used supportive care drugs in cancer patients.

Key resources for evaluating PGx effect on drug exposure–response

The Clinical Pharmacogenetics Implementation Consortium (CPIC) is a network of PGx experts who curate PGx data identified in the primary literature and develop guidelines on how to translate PGx test results into actionable

prescribing decisions [14]. The Pharmacogenomics Knowledgebase (PharmGKB) is another comprehensive resource that curates knowledge about the impact of genetic variation on drug response [15]. The Pharmacogene Variation (PharmVar) Consortium is a central repository for PGx variation that focuses on haplotype structure and allelic variation [16]. PGx efforts are synchronized between PharmVar, PharmGKB, and CPIC, providing clinicians, researchers, labs, and payers critical resources for evaluating the clinical actionability of drug-gene interactions.

The US Food and Drug Administration (FDA) has also published a table of pharmacogenetic associations in February 2020, which is meant to provide the agency's stance on the state of the science in PGx [17]. The table categorizes drug-gene interactions into three sections of PGx associations: those for which the data support therapeutic management recommendations; those for which the data indicate a potential impact on safety or response; and those for which the data demonstrate a potential impact on pharmacokinetic properties only.

Awareness of and knowledge on how to apply these resources to integrate PGx information into medication management processes are critical. It is important to recognize there are some differences in recommendations between the FDA and CPIC/PharmGKB; however, these groups likely utilize different sources of information for making PGx-based recommendations and thus should be used holistically in the context of the entire patient to determine optimal pharmacotherapy management.

Supportive care PGx

Several supportive therapies for cancer-related symptoms are prone to PGx variation and could result in under or overexposure. For example, ondansetron is one of the most widely prescribed antiemetics for cancer patients. Ondansetron is partly inactivated by CYP2D6, and ultrarapid metabolizers may be at risk for underexposure. Studies have suggested these patients may have increased rates of breakthrough nausea/vomiting [18]. CPIC guidelines suggest alternative therapies, such as granisetron, which is not metabolized by CYP2D6 [19]. Further, the haplotype *ABCB1* is related to increased risk of delayed emesis but not in the acute phase, whereas polymorphisms in *OCT1* may increase the efficacy of tropisetron and ondansetron [20, 21]. Further studies are required to validate the role of these drug transporters on drug response.

Many cancer populations are at risk for infections due to being heavily immunosuppressed, especially those undergoing hematopoietic cell transplantation. Voriconazole, a commonly used azole antifungal, is inactivated by CYP2C19. About one-third of Caucasians and African Americans carry

the *17 allele which results in increased enzyme activity. CYP2C19 rapid and ultrarapid metabolizers have a higher likelihood of underexposure and thus increased risk of breakthrough fungal infections [22]. CPIC guidelines suggest using an alternative antifungal in these patients (as well as in poor metabolizers due to increased toxicity risk) [23], but genotype-guided dosing trials have also shown administration of higher up front voriconazole doses can normalize trough levels without increasing toxicity risk [24, 25].

Pain is one of the most commonly reported symptoms by patients with cancer. Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly prescribed for mild to moderate pain, while more severe pain is typically treated with opioids. Most NSAIDs are hepatically metabolized by CYP2C9, 1A2, and 3A4, before renal clearance. *CYP2C9* genotype is associated with phenotypic variability, which alters drug metabolism and plasma NSAID concentrations. Studies have identified an association between decreased and no function alleles with increased drug exposure and toxicity risk [26]. Depending on the specific NSAID, CPIC guidelines recommend dose adjustments in certain intermediate and poor metabolizers [26].

Some opioids, on the other hand, are metabolized by CYP2D6 to active, more potent, metabolites. For example, codeine and tramadol require activation by CYP2D6 to morphine and o-desmethytramadol, respectively. CYP2D6 poor metabolizers are at risk of underexposure of the active metabolite and thus reduced analgesia, whereas ultrarapid metabolizers are at risk of overexposure and increased toxicity. CPIC guidelines suggest using an alternative opioid not metabolized by CYP2D6 [27]. Of note, hydrocodone and oxycodone have varying levels of CYP2D6-mediated metabolism and may be prone to PGx variation, although the data is less clear. Pharmacodynamic based genes, such as those encoding for the mu-opioid receptor (*OPRM1*) and catechol-O-methyltransferase (*COMT*), may also affect opioid sensitivity and morphine equivalents required for pain relief, although guidelines suggest these are not actionable and dosing should be based on tolerability alone [27].

Proton pump inhibitors (PPIs) are also frequently used in cancer patients to combat acid reflux and other gastrointestinal-related complications. Most PPIs (omeprazole, lansoprazole, pantoprazole, and dexlansoprazole) are metabolized and inactivated by CYP2C19. Rapid and ultrarapid metabolizers are at higher risk of underexposure and increased risk of therapeutic failure. CPIC guidelines suggest increasing the starting daily dose by up to 100% [28]. Alternatively, intermediate and poor metabolizers are at risk of overexposure and related side effects. The guidelines recommend starting with standard dosing, but for chronic therapy consider a 50% dose reduction to avoid long-term complications.

Lastly, psychotropics are commonly prescribed to cancer patients experiencing depressive symptoms. Many selective serotonin reuptake inhibitors (SSRIs), including citalopram, escitalopram, and sertraline, are also inactivated by CYP2C19. Similar to PPIs and voriconazole, rapid and ultrarapid metabolizers are at risk of underexposure and therapeutic failure, whereas poor and intermediate metabolizers are at risk for overexposure and drug-related side effects. Other antidepressants are metabolized by CYP2D6, including paroxetine and vortioxetine. Some, like tricyclic antidepressants (TCAs), may be metabolized by both CYP2C19 and CYP2D6. Numerous pharmacokinetic studies have confirmed the impact of *CYP2C19* and *CYP2D6* genetic variation on drug concentrations for various psychotropics [29]. Subsequently, randomized trials have suggested that PGx-guided antidepressant selection can improve response and remission rates [30]. CPIC guidelines provide specific drug and dose selection recommendations for SSRIs and TCAs [31].

Drug interactions/phenoconversion

Potential metabolic drug interactions within supportive care drug combinations and between the supportive care drugs and cytotoxics must be considered. An instructive example is antiemetic prophylaxis where triple antiemetic therapy with a 5-hydroxytryptamine₃ receptor inhibitor, a neurokinin₁ inhibitor, and dexamethasone is the evidence-based recommendation for chemotherapy combinations of high emetic potential [32]. Aprepitant, or its intravenous formulation fosaprepitant, is a moderate inhibitor of CYP3A4. This increases the AUC of dexamethasone 2.2-fold, which means that with concomitant use, the dose of dexamethasone should be halved to reduce dexamethasone toxicity [33]. There is no clinically important interaction reported with ondansetron. To date, there have not been obvious interactions between aprepitant or fosaprepitant and chemotherapy drugs such as the taxanes, etoposide, irinotecan, the vinca alkaloids, and imatinib which are also metabolized by CYP3A4. However, aprepitant has a small measurable inhibitory effect on the activation of cyclophosphamide and the metabolism of thiotepa [34].

Drugs potentially used concomitantly with cancer therapy, which are strong CYP3A4 inducers, include rifampicin and unorthodox therapies such as St John's Wort, which will reduce the concentration of aprepitant, whereas strong inhibitors such as ketoconazole can increase the AUC of aprepitant up to fivefold. Aprepitant also induces the metabolism of drugs metabolized by CYP2C9 which requires careful monitoring of drugs such as warfarin, phenytoin, and tolbutamide [33, 34].

Lastly, phenoconversion refers to the ability of moderate to strong inhibitors to convert genotypic normal metabolizers into phenotypic intermediate or poor metabolizers of drugs metabolized by that enzyme [35]. For example, several antidepressants like paroxetine, fluoxetine, and bupropion are strong CYP2D6 inhibitors. Concomitant use of these medications can convert genotypic normal metabolizers into phenotypic poor metabolizers, which could have drastic effects on drugs metabolized by CYP2D6, including opioids, but also anticancer therapies like tamoxifen, thus resulting in poorer patient outcomes.

Conclusion/future directions

Treatment decisions in oncology must be understood in the context of the broader cancer care continuum, from screening, suspicion of disease, diagnostic work-up, diagnosis, staging, treatment selection, supportive care, post-treatment rehabilitation and follow-up, and palliative and end-of-life care. More than ever, decision-making today is more complex. The advent and expansion of innovative diagnostic tests, including NGS platforms that provide understanding of the molecular attributes of the cancer, genetic tests performed to determine potential hereditary genes driving cancer cell proliferation, and pre-emptive PGx testing to determine individual patient's capacity to metabolize both treatment and supportive agents are all fundamental now to improving outcomes and mitigating toxicities. Moreover, the costs of these tests have reduced in recent years. While clinicians must make decisions based on assessment of cost and benefit to the patient, the cost effectiveness of avoiding ineffective drugs or drugs that produce greater toxicity that might result in expensive emergency department visits or hospitalizations will result in greater acceptance of and use of these tests to inform treatment and supportive care decision-making. The involvement of the epigenome, transcriptome, proteome, metabolome, and microbiome further complicates the effect of genomics on drug response and toxicity.

We recognize the enormous complexity of data emerging from molecular testing. Making sense of these data is difficult enough, especially in a timely manner. Couple sequencing, hereditary germline testing, and PGx testing with other patient data, including co-morbid conditions, current medications and drug interactions, allergies, fitness, nutrition, and psychosocial status exceed the ability of a busy community oncologist to process these data in real time. Artificial intelligence (AI) platforms, including expert-based systems and those architected with machine learning capability, are no longer the future. AI platforms are essential today to ensure consistent application of evidence-based guidelines and practice in an era of highly complex oncology care.

Declarations

Conflict of interest The authors declare no competing interests.

References

1. Rapoport BL, Anderson R (eds) (2020) Special section: the multinational association of supportive care in cancer (MASCC) 2020 Clinical practice recommendations for the management of immune-mediated adverse events from checkpoint inhibitors. *Supp Care Cancer* 28. <https://doi.org/10.1007/s00520-020-05728-y>
2. Patel JN (2021) Opportunities for pharmacogenomics-guided supportive care in cancer. *Supp Care Cancer* 29:555–557. <https://doi.org/10.1007/s00520-020-05892-1>
3. Martin JH, Olver IN (2021) Precision medicine-based drug treatment individualisation in oncology. *Br J Clin Pharmacol* 87:223–226. <https://doi.org/10.1111/bcp.14512>
4. Gasche Y, Daali Y, Fathi M, Chiappe A, Cottini S, Dayer P, Desmeules J (2004) Codeine intoxication associated with ultrarapid CYP2D6 metabolism. *N Engl J Med* 351:2827–2831. <https://doi.org/10.1056/NEJMoa041888>
5. Innocenti F, Mills SC, Sanoff H, Ciccolini J, Lenz HJ, Milano G (2020) All you need to know about DPYD genetic testing for patients treated with fluorouracil and capecitabine: a practitioner-friendly guide. *JCO Oncol Pract* 16(12):793–798. <https://doi.org/10.1200/OP.20.00553>
6. Andrews MC, Duong CPM, Gopalakrishnan V et al (2021) Gut microbiota signatures are associated with toxicity to combined CTLA-4 and PD-1 blockade. *Nat Med*. <https://doi.org/10.1038/s41591-021-01406-6>
7. Carr DF, Turner RM, Pirmohamed M (2021) Pharmacogenomics of anticancer drugs: personalising the choice and dose to manage drug response. *Br J Clin Pharmacol* 83:237–255. <https://doi.org/10.1111/bcp.14407>
8. Sprangers B, Sandhu G, Rosner MH, Tesarova P, Stadler WM, Malyszko M (2020) Drug dosing in cancer patients with decreased kidney function: a practical approach. *Cancer Treat Rev* 93:10139. <https://doi.org/10.1016/j.ctrv.2020.102139>
9. Brixner D, Biltaji E, Bress A, Unni S, Ye X, Mamiya T, Ashcraft K, Biskupiak J (2016) The effect of pharmacogenomic profiling with a clinical decision support tool on healthcare resource utilization and estimated costs in the elderly exposed to polypharmacy. *J Med Econ* 19(3):213–228. <https://doi.org/10.3111/13696998.2015.1110160>
10. Tsuji D, Matsumoto M, Kawasaki Y, Kim Y-IL, Yamamoto K, Nakamichi H, Sahara Y, Makuta R, Yokoi M, Miyagi T, Itoh K (2021) Analysis of pharmacogenomic factors for chemotherapy-induced nausea and vomiting in patients with breast cancer receiving doxorubicin and cyclophosphamide chemotherapy. *Cancer Chemother Pharmacol* 87:73–83. <https://doi.org/10.1007/s00280-020-04177-y>
11. Dai HD, Vugmeyster Y, Mangal N (2020) Characterizing exposure-response relationship for therapeutic monoclonal antibodies in immuno-oncology and beyond: challenges, perspective, and prospects. *Clin Pharmacol Therap* 108(6):1156–1170. <https://doi.org/10.1002/cpt.1953>
12. Palmer J, McCune JS, Perales M, Marks D, Bubalo J, Mohty M, Wingard JR, Paci A, Hassan M, Bredeson C, Pidala J, Shah N, Shaughnessy P, Majhail N, Schriber J, Savani BN, Carpenter PA (2016) Personalizing busulfan-based conditioning: considerations from the American Society for Blood and Marrow Transplantation Practice Guidelines Committee. *Biol Blood Marrow Transpl* 22:1915–1925. <https://doi.org/10.1016/j.bbmt.2016.07.013>

13. Wang L, McLeod HL, Weinshilboum RM (2011) Genomics and drug response. *N Eng J Med* 364:1144–1153. <https://doi.org/10.1056/NEJMr1010600>
14. Relling MV, Klein TE (2011) CPIC: Clinical pharmacogenetics implementation consortium of the pharmacogenomics research network. *Clin Pharmacol Ther* 89(3):464–467
15. Whirl-Carrillo M, McDonagh EM, Hebert JM, Gong L, Sangkuhl K, Thorn CF, Altman RB, Klein TE (2012) Pharmacogenomics knowledge for personalized medicine. *Clin Pharmacol Ther* 92(4):414–417. <https://doi.org/10.1038/clpt.2010.279>
16. Gaedigk A, Ingelman-Sundberg M, Miller NA, Leeder SJ, Whirl-Carrillo M, Klein TE, PharmVar Steering Committee (2018) The Pharmacogene Variation (PharmVar) Consortium: incorporation of the human cytochrome P450 (CYP) allele nomenclature database. *Clin Pharmacol Ther* 103(3):399–401. <https://doi.org/10.1002/cpt.910>
17. United States Food and Drug Administration. Table of pharmacogenetic associations. Accessed June 17 2021. (<https://www.fda.gov/medical-devices/precision-medicine/table-pharmacogenetic-associations>)
18. Trammel M, Roederer M, Patel JN, McLeod HL (2013) Does pharmacogenomics account for variability in control of acute chemotherapy-induced nausea and vomiting with 5-hydroxytryptamine-3 receptor antagonists? *Curr Oncol Rep* 15(3):276–285
19. Bell GC, Caudle KE, Whirl-Carrillo M, Gordon RJ, Hikino K, Prows CA, Gaedigk A, Agundez J, Sadhasivam S, Klein TE, Schwab M (2017) Clinical Pharmacogenetics implementation consortium (CPIC) guideline for CYP2D6 genotype and use of ondansetron and tropisetron. *Clin Pharmacol Ther* 102(2):213–218. <https://doi.org/10.1002/cpt.598>
20. Perwitasari DA, Wessels JAM, van der Straaten RJHM, Baak-Pablo RF, Mustofa M, Hakimi M, Nortie JWR, Gelderblom H, Guchelaar H-J (2011) Association of ABCB1, 5-HT3B Receptor and CYP2D6 genetic polymorphisms with ondansetron and metoclopramide antiemetic response in Indonesian cancer patients treated with highly emetogenic chemotherapy. *Jpn J Clin Oncol* 41:1168–1176. <https://doi.org/10.1093/jjco/hyr117>
21. Tzvetkov MV, Saadatmand AR, Bokelmann K, Meinke I, Kaiser R, Brockmüller J (2012) Effects of OCT1 polymorphisms on the cellular uptake, plasma concentrations and efficacy of the 5-HT₃ antagonists tropisetron and ondansetron. *Pharmacogenomics J* 12:22–29. <https://doi.org/10.1038/tpj.2010.75>
22. Owusu Obeng A, Egelund EF, Alsultan A, Peloquin CA, Johnson JA (2014) CYP2C19 polymorphisms and therapeutic drug monitoring of voriconazole: are we ready for clinical implementation of pharmacogenomics? *Pharmacotherapy* 34:703–718. <https://doi.org/10.1002/phar.1400>
23. Moriyama B, Owusu Obeng A, Barbarino J et al (2016) Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for CYP2C19 and voriconazole therapy. *Clin Pharmacol Ther* 102:45–51. <https://doi.org/10.1002/cpt.583>
24. Patel JN, Hamadeh IS, Robinson M et al (2020) Evaluation of CYP2C19 genotype-guided voriconazole prophylaxis after allogeneic hematopoietic cell transplant. *Clin Pharmacol Ther* 107(3):571–579. <https://doi.org/10.1002/cpt.1642>
25. Hicks JK, Quilitz RE, Komrokji RS et al (2020) Prospective CYP2C19-guided voriconazole prophylaxis in patients with neutropenic acute myeloid leukemia reduces the incidence of subtherapeutic antifungal plasma concentrations. *Clin Pharmacol Ther* 107(3):563–570. <https://doi.org/10.1002/cpt.1641>
26. Theken KN, Lee CR, Gong L, Caudle KE, Formea CM, Gaedigk A, Klein TE, Agundez JAG, Grosser T (2020) Clinical Pharmacogenetics Implementation consortium guideline (CPIC) for CYP2C9 and nonsteroidal anti-inflammatory drugs. *Clin Pharmacol Ther* 108(2):191–200. <https://doi.org/10.1002/cpt.1830>
27. Crews KR, Monte AA, Huddart R et al (2021) Clinical pharmacogenetics implementation consortium guideline for CYP2D6, OPRM1, and COMT genotypes and select opioid therapy. *Clin Pharmacol Ther*. <https://doi.org/10.1002/cpt.2149>
28. Lima JJ, Thomas CD, Barbarino J et al (2020) Clinical pharmacogenetics implementation consortium (CPIC) guideline for CYP2C19 and proton pump inhibitor dosing. *Clin Pharmacol Ther*. <https://doi.org/10.1002/cpt.2015>
29. Stingl JC, Brockmoller J, Viviani R (2013) Genetic variability of drug-metabolizing enzymes: the dual impact on psychiatric therapy and regulation of brain function. *Mol Psychiatry* 18(3):273–287. <https://doi.org/10.1038/mp.2012.42>
30. Bousman CA, Arandjelovic K, Mancuso SG, Eyre HA, Dunlop BW (2019) Pharmacogenetic tests and depressive symptom remission: a meta-analysis of randomized controlled trials. *Pharmacogenomics* 20(1):37–47. <https://doi.org/10.2217/pgs-2018-0142>
31. Hicks JK, Bishop JR, Sangkuhl K, Muller DJ, Ji Y, Leckband SG, Leeder JS, Graham RL, Chiulli DL, Llerena A, Skaar TC, Scott SA, Stingl JC, Klein TE, Caudle KE, Gaedigk A, Clinical pharmacogenetics implementation C (2015) Clinical pharmacogenetics implementation consortium (CPIC) guideline for CYP2D6 and CYP2C19 genotypes and dosing of selective serotonin reuptake inhibitors. *Clin Pharmacol Ther* 98(2):127–134. <https://doi.org/10.1002/cpt.147>
32. Roila F, Molassiotis A, Herrstedt J, Aapro M, Gralla RJ, Bruera E, Clark-Snow RA, Dupuis LL, Einhorn LH, Feyer P, Hesketh PJ, Jordan K, Olver I, Rapoport BL, Ruhlmann CH, Walsh D, Warr D, van der Wetering M (2016) MASCC and ESMO guideline update for the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting and of nausea and vomiting in advanced cancer patients. *Ann Oncol* 27(Suppl 5):v119–v133
33. Olver IN (2008) Prevention of chemotherapy-induced nausea and vomiting: focus on fosaprepitant. *Ther Clin Risk Manag* 4:1–6
34. Schoffelen R, Lankheet AG, van Herpen CML, van der Hoven JJM, Desart IME, Kramers C (2018) Drug-drug interactions with aprepitant in antiemetic prophylaxis for chemotherapy. *Neth J Med* 76:109–114
35. Shah RR, Smith RL (2015) Addressing phenoconversion: the Achilles' heel of personalized medicine. *Br J Clin Pharmacol* 79(2):222–240. <https://doi.org/10.1111/bcp.12441>

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.