Diagnostic Snapshot

Can a Benign Hematology Phenomenon Critically Impact the Neutropenia Status and Treatment of Patients With Cancer?

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Authors' disclosures of conflicts of interest are found at the end of this article.

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Abstract

Neutropenia in oncology care usually has a disease-related or therapy-related etiology. However, for a population with a benign hematology phenomenon known as benign ethnic neutropenia (BEN) or Duffy-null associated neutrophil count (DANC), neutropenia can be unexpected or more severe during oncology care. A lack of awareness of this phenomenon and its impact can lead to actions that result in treatment delays, dose reductions, or even treatment discontinuation. Additionally, patients may be excluded from clinical trials, and neutropenia may be inaccurately graded as an adverse event or used incorrectly as a criterion for remission status due to the reference range for neutrophil counts often based on values for individuals without BEN/DANC. The population with BEN/DANC also overlaps with historically underserved groups in health care, further highlighting the urgency of raising awareness about the effects of BEN/DANC in cancer care. This presentation emphasizes the critical impact BEN/DANC plays in the neutropenia status in some oncology patients and proposes a new algorithm that advanced practitioners (APs) can use to identify BEN/DANC during initial cancer evaluation for optimization of time-sensitive and dose-sensitive therapies.

HISTORY AND PHYSICAL

A man in his 50s diagnosed with a gastrointestinal cancer was undergoing treatment with an immune checkpoint inhibitor (ICI). Three months into his treatment, he developed grade 3 neutropenia with an absolute neutrophil count (ANC) less than 1.0 × 10^9 cells/L or 1,000/μL. His platelets and hemoglobin were normal. He had no neutropenia prior to the start of his cancer treatment.

A detailed history and physical revealed that the patient was Black of African ancestry and his family and social histories were unremarkable concerning neutropenia. In his past medical history, his primary care physician noted occasional low white blood cell (WBC) count in his annual checkups. However, because he had no illnesses, he was told that he likely had a benign neutropenia seen in many people of African descent. Therefore, a referral was not made to evaluate previous neutropenia. The patient also did not have other health complications and was not undergoing concurrent therapies.

FURTHER ASSESSMENT: BENIGN HEMATOLOGY CONSULT

A peripheral blood smear was ordered to assess the morphology and count of the blood cells. Cobalamin, copper, and serum methylmalonic acid (MMA) levels were tested for vitamin and mineral deficiencies. A red blood cell (RBC) test called "RBC antigen genotyping" test or "RBC antigens molecular methods" test was ordered. It detects the presence of the Fy(a-b-) phenotype, which supports the diagnosis of BEN/DANC (Elhadad et al., 2022; Gay et al., 2023; Merz et al., 2023).

Neutrophils are one of the five types of WBCs and are the most abundantly produced, accounting for 40% to 70% of the total WBC count. However, only a small fraction of neutrophils circulates in the peripheral blood, as the majority remain in the bone marrow. The absolute neutrophil count (ANC) normally ranges from 1.8 to 7.5 × 10^9 cells/L or 1,800 to 7,500/µL (Awan et al., 2021).

DIFFERENTIAL DIAGNOSIS

WHAT IS THE CORRECT DIAGNOSIS?

- A ☐ Therapy-induced neutropenia
- B ☐ Neutropenia secondary to coexisting health conditions
- C ☐ Neutropenia of malignant etiology
- C ☐ Neutropenia of benign hematology etiology

SEE PAGE 3 FOR ANSWER ▶

THE CORRECT DIAGNOSIS IS:

A. Therapy-induced neutropenia

B. Neutropenia secondary to coexisting health conditions

C. Neutropenia of malignant etiology

D. Neutropenia of benign hematology etiology (correct answer)

DISCUSSION

A Therapy-induced neutropenia. Although neutropenia is a common adverse event of many cancer therapies, this patient is receiving a single immunotherapy agent of the class of drugs called ICIs, which carries a low risk of neutropenia compared to chemotherapy agents. Immune checkpoint inhibitor–induced neutropenia was also ruled out in part because another differential was ruled in. The neutropenia could also be due to peripheral destruction caused by drugs such as haptens (aminopyrine, α-methyldopa, phenylbutazone, mercurial diuretics, some phenothiazines). However, this patient was not taking any of these medications (Holland & Gallin, 2022).

B Neutropenia secondary to coexisting health conditions. Neutropenia can result from decreased neutrophil production due to non-cytotoxic agents such as antibiotics (e.g., sulfas, penicillins), antipsychotics (e.g., clozapine), anti-inflammatory or antithyroid drugs, as well as infections (e.g., AIDS, hepatitis, HIV, Epstein-Barr virus, bacterial, parasitic, and rickettsial infections, tuberculosis, typhoid fever, brucellosis, malaria, viral hepatitis, or leishmaniasis), or nutritional deficiencies (e.g., vitamin B12 or folate in cases of alcoholism). However, this patient was not experiencing any of these conditions, and his cobalamin, copper, and serum MMA levels were normal.

Transient neutropenia can occur due to peripheral pooling, as seen in cases of overwhelming bacterial infection, hemodialysis, or cardiopulmonary bypass; however, this was not the case for this patient. Neutropenia can also result from peripheral destruction caused by antineutrophil antibodies, leading to the redistribution of neutrophils in the vascular endothelium, spleen, or lungs (splenic or lung trapping). It can also be associated with autoimmune or rheumatologic disorders, such as Felty syndrome, rheumatoid arthritis, lupus erythematosus, or granulomatosis with polyangiitis (Wegener's). This patient had not experienced any of these conditions (Berliner, 2022; Holland & Gallin, 2022).

C Neutropenia of malignant etiology. Neutropenia can occur in cases of aplastic anemia, but other cytopenias typically present alongside it. In addition, the patient's previous neutropenia events resolved spontaneously. He had not received treatments that could lead to a secondary malignancy presenting with neutropenia. Tumor invasion of the bone marrow, such as in myelofibrosis, can impact neutrophil production; however, this was unlikely, as the other complete blood count values were normal. Therefore, a bone marrow evaluation was not ordered to avoid potential iatrogenic harm (Berliner, 2022; Holland & Gallin, 2022).

D Neutropenia of benign hematology etiology (correct answer). This patient was of African ancestry, with previous reports of occasional asymptomatic neutropenia. His primary care physician had mentioned BEN as a possible cause, although no testing was conducted to confirm this diagnosis. Neutropenia starts with ANC less than 1.8×10^9 cells/L or 1,800/μL in some reference ranges or less than 1.5×10^9 cells/L or 1,500/μL in other reference ranges. Individuals with BEN/DANC may have an asymptomatic low ANC of 1.2×10^9 cells/L or 1,200/μL, or approximately 40% less neutrophil in the peripheral circulation than others (Hantel et al., 2024; Morrissey, 2024).

Benign ethnic neutropenia was first reported in Black individuals of African descent by Forbes and colleagues in 1941. Now called Duffy-null associated neutrophil count (DANC), Berliner (2022) describes it as an inherited mild-to-moderate neutropenia in individuals of African descent and certain other ethnic groups, which is not linked to an

increased risk of infections. It is a normal variant where the neutrophil count is less than 1.5×10^9 cells/L or 1,500/µL with no recurrent or severe infections, other cytopenias, or associated illnesses. Duffy-null associated neutrophil count is associated with the Duffy-null Fy(a-b-) RBC phenotype and is also sometimes referred to as Duffy-null phenotype-associated neutropenia (Gay et al., 2023).

Scientists are moving away from calling it BEN and instead are referring to it as DANC, as the term "benign" implies an abnormality, whereas DANC reflects a normal, healthy variant. Using DANC instead of BEN helps "depathologize" the variant by associating it with a biological marker rather than race or ethnicity. Additionally, scientists argue that the term "ethnic" is misleading, as not all individuals within an ethnic group known to have BEN/DANC will be diagnosed with it (Merz et al., 2023).

PREVALENCE OF BEN/DANC

As shown in Figure 1, BEN/DANC is prevalent among Africans and people of African descent from the diaspora (Caribbean, West Indies), occurring in approximately 25% to 50% of individuals. It is observed in approximately 4.5% of African Americans, 10.7% in Arabs and some individuals from the Middle East (Israeli Bedouins, Jordanians, and natives of the United Arab Emirates), 11.8% of Yemenite Jews, 15.4% of Black Ethiopian Jews, some individuals from the Mediterranean area such as those of Greek descent, and some individuals from South America, and in less than 1% of the White population in the US (Awan et al., 2021; Berliner, 2022; Elhadad et al., 2022; Morrissey, 2024).

GENETIC ETIOLOGY OF BEN/DANC

A polymorphism on chromosome 1q22.239 contains the Duffy antigen receptor for chemokines (DARC) gene, also known as the atypical chemokine receptor 1 (*ACKR1*) gene. This gene includes a single nucleotide polymorphism (SNP), rs2814778, which results in a nonfunctional allele (Gay et al., 2023). The SNP rs2814778 resides in the promoter region of the DARC gene that prevents transcription and results in the RBC Duffy-null phenotype Fy(a-b-) (Merz et al., 2023). Therefore, individuals with BEN/DANC exhibit homozygosity for the SNP of the DARC/ACKR1 gene called rs2814778. DARC is broadly

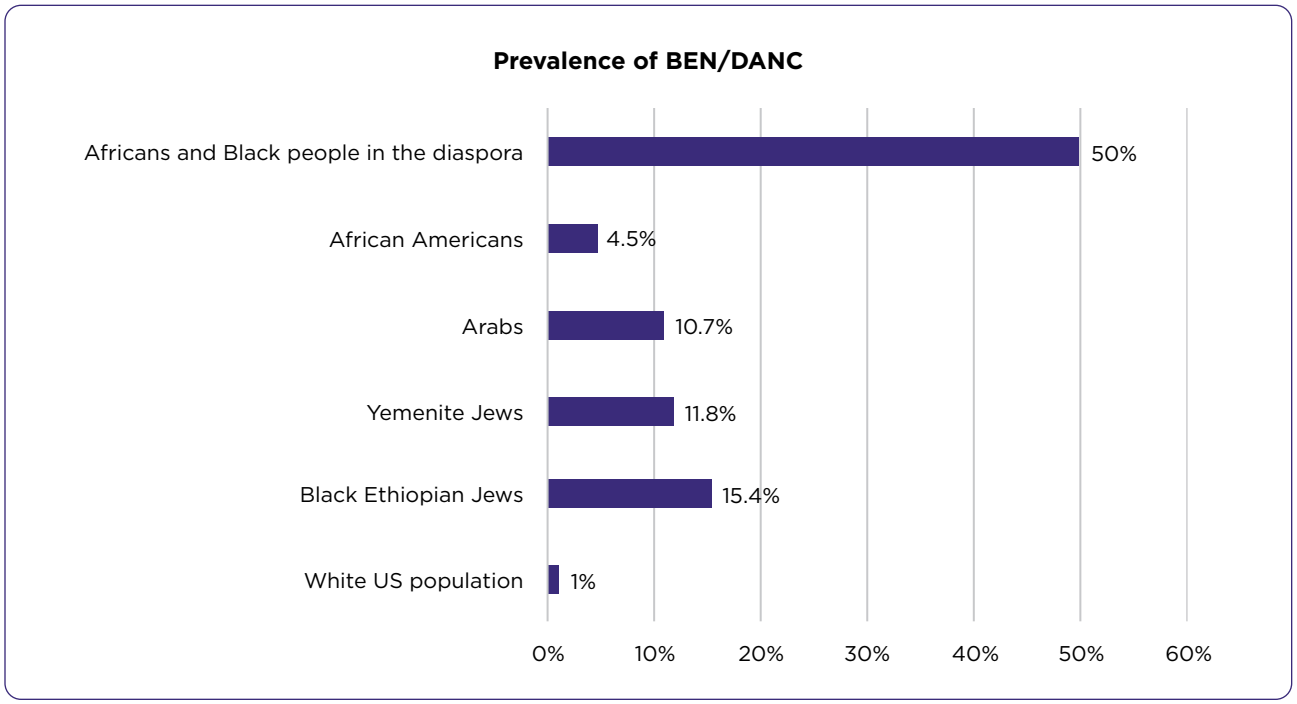

Figure 1. Prevalence of benign ethnic neutropenia (BEN)/Duffy-null associated neutrophil count (DANC). Information from Awan et al. (2021); Berliner (2022); Elhadad et al. (2022); Morrissey (2024).

Table 1. Result of RBC Antigens Molecular Methods Test Showing Fya- and Fyb- Phenotype That Confirms BEN/DANC

Phenotype Value S-	Phenotype Value A1(TNP)	
Phenotype Value Jsb+	Phenotype Value LWb-	
Phenotype Value e+.	Phenotype Value Fya-	✓
Phenotype Value Jka+	Phenotype Value c+.	
Phenotype Value HgbS-	Phenotype Value Fyb-	✓
Phenotype Value E-	Phenotype Value Kpa-	

Note. BEN/DANC = benign ethnic neutropenia/Duffy-null associated neutrophil count; RBC = red blood cell.

expressed on RBCs, kidney, brain, and endothelial cells but is not found on leukocytes. The DARC protein on RBCs is expressed as a transmembrane glycoprotein known as the Duffy blood group antigen (Fy). This protein acts as a "cytokine sink," binding to inflammatory cytokines. As a result, Duffy-null RBCs are less effective at attracting neutrophils into the periphery. Additionally, the SNP rs2814778 affects hematopoiesis and results in phenotypically distinct neutrophils that readily leave the periphery (Merz et al., 2023). Another mechanism is a rapid egress of activated DARC-null neutrophils from circulation to the spleen. Neutrophil function remains normal, while in DARC-null HIV-1 patients with BEN/DANC, a lack of recurrent and/or serious infections is noted (Gay et al., 2023). Figure 2 summarizes the genetic mechanism of BEN/DANC.

CASE STUDY CONTINUED

Benign hematology, also called classical hematology, was consulted to evaluate the neutropenia of nonmalignant etiology. A referral was expedited to prevent a long interruption of treatment. The results in the following week showed that the peripheral blood smear was normal. Cobalamin, copper, and serum MMA were normal. The RBC antigen genotyping test or RBC antigens molecular methods test confirmed the Duffy-null status associated with BEN/DANC by evidencing the Duffy-null RBC Fy(a-b-) phenotype.

Table 1 displays the RBC antigen genotyping test result of this patient and shows both Fya- and Fyb- phenotype, which are evidence of BEN/DANC status.

TREATMENT

The benign hematologist recommended resuming cancer treatment since the patient was asymptomatic and the BEN/DANC status was confirmed. They also recommended for as-needed use of granulocyte colony-stimulating factor (G-CSF) if neutropenia reached grade 4 with ANC less than 0.5×10^9 cells/L or 500/μL.

DISCUSSION: AWARENESS AND IMPACT OF BEN/DANC

In this case, the cancer therapy was interrupted for 1 week while the neutropenia was evaluated. However, if the patient's BEN/DANC status had been previously confirmed, the therapy interruption would have been avoided. Table 2 highlights ways in which BEN/DANC has implications for patient care, with instances of treatments being held, delayed, or dose reduced.

IMPLICATIONS FOR ONCOLOGY ADVANCED PRACTITIONERS

The success of cancer treatments relies a great deal on timeliness and efficacy of therapeutic agents. Delays, interruptions, or dose reductions trigger concern for the negative effects on patient outcomes. Clarifying BEN/DANC status during the initial cancer evaluation will strengthen evidence-based clinical practice that fosters population-based, patient-centered care and enhance the oncology care paradigm. Hantel and colleagues (2024) and Morrissey (2024) highlighted that the BEN/DANC status has become a source of discrimination in cancer research and care practices.

The first step in improving this situation is to promptly clarify the BEN/DANC status of new cancer patients within this specific population, as outlined in Figure 3 of the new algorithm titled "Algorithm for Clarification of the BEN/DANC Status to Prevent Disruptions During Cancer

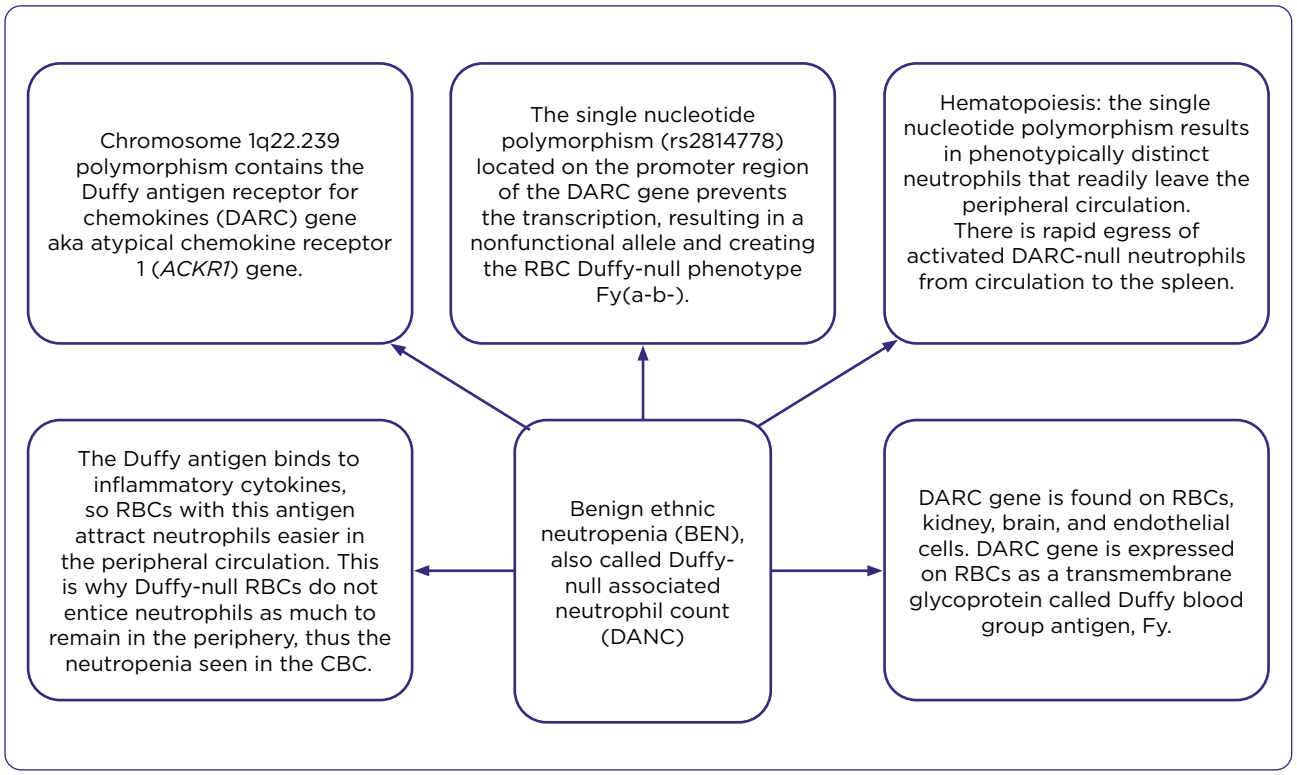

Figure 2. Genetic mechanism of neutropenia in benign ethnic neutropenia (BEN)/Duffy-null associated neutrophil count (DANC). Information from Elhahdad et al. (2022); Gay et al. (2023); Merz et al. (2023).

Table 2. Literature Review of the Implications of Benign Ethnic Neutropenia (BEN)/Duffy-Null Associated Neutrophil Count (DANC) for Patient Care

Author	Finding
Gay et al., 2023	• Duffy phenotyping would give parents and patients reassurance along with decreasing overall health-care costs by eliminating additional tests and future consults. • Increasing the use of Duffy typing in asymptomatic patients may decrease the need for frequent laboratory testing and evaluation by hematology-oncology.
Hantel et al., 2024; Morrissey, 2024	• Source of discrimination in cancer care: ANC as low as $< 1.2 \times 10^9$ cells/L or 1,200/µL is common in BEN/DANC patients and is exclusionary for many clinical trials, leading to inaccurate grading of adverse events and remission status.
Merz et al., 2023; Mpofu et al., 2021	• Exclusion from critical trials due to ANC requirement > 1,500 cells/µL has been observed for clinical trials for HIV vaccines.
Lynce et al., 2021; Hantel et al., 2024; Morrissey, 2024	• Potential for suboptimal therapy: adherence to standard neutropenia guidelines can lead to dose reductions for individuals with BEN/DANC and cause inaccurate adverse events grading and remission status categorization.
Lynce et al., 2021	• Dose reductions were observed for Black women with Duffy-null status who were undergoing breast cancer therapy with palbociclib.
Merz et al., 2023	• In rheumatology, azathioprine discontinuation for lower ANC is higher in Black Duffy-null patients.
Andreou et al., 2023; Tirupati et al., 2020; Wu et al., 2024	• In psychiatry, clozapine, the only drug for treatment-resistant schizophrenia with a 30% prevalence, is underutilized in the BEN/DANG population due in part to hematologic concerns including neutropenia.

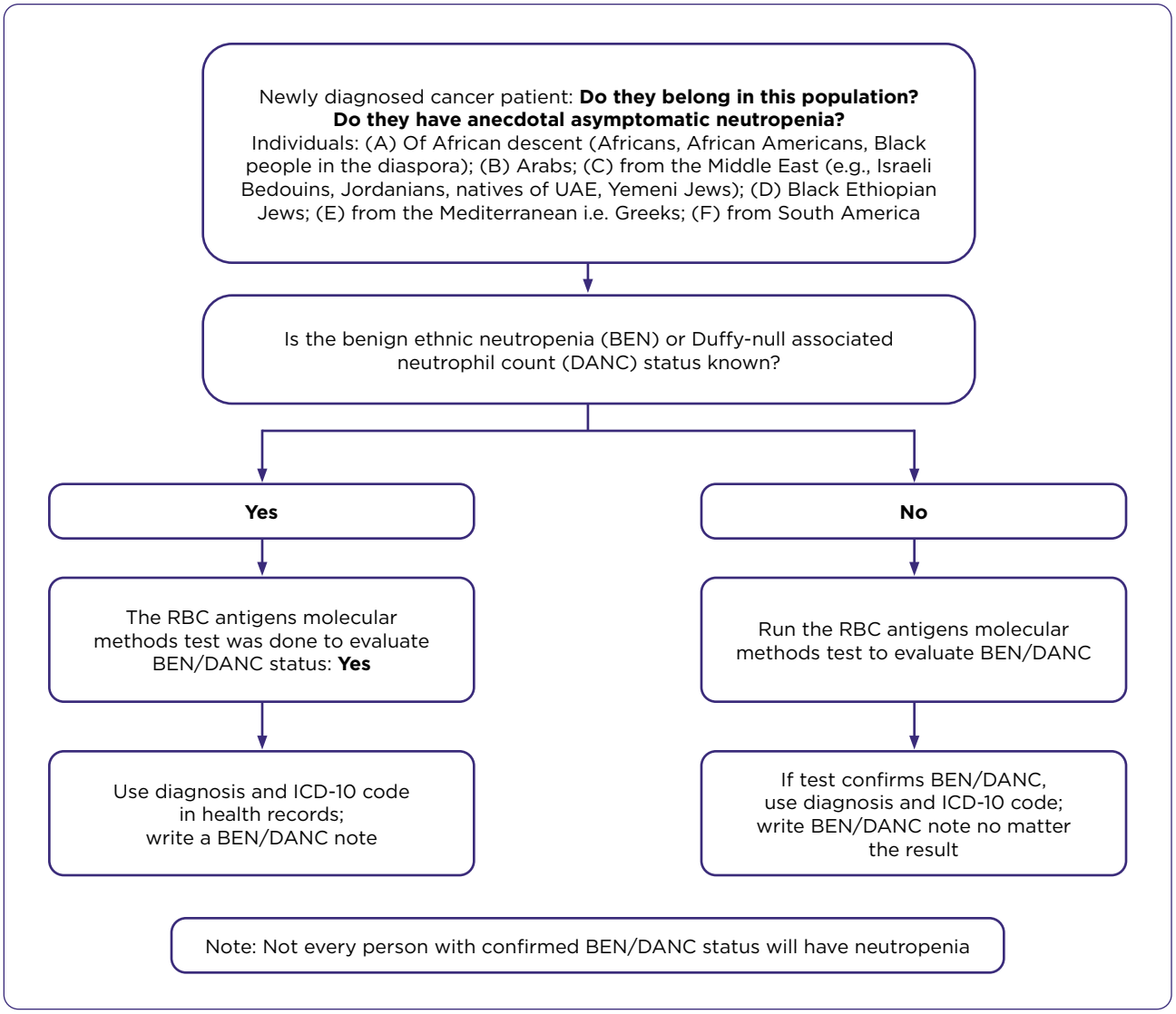

Figure 3. Algorithm for clarification of the BEN/DANC status to prevent disruptions during cancer treatments. UAE = United Arab Emirates.

Treatments." Documenting the BEN/DANC status in the medical record will serve as a constant reminder to the clinical team to remain vigilant in preventing therapy disruptions that can hinder the optimization of oncology care for this patient population.

CONCLUSION

For a certain population, a cancer diagnosis can be significantly impacted by an inherited classical hematologic condition known as BEN/DANC. Patients with BEN/DANC receiving cancer therapies often experience delays, interruptions, dose reductions, exclusion from clinical trials, and inaccurate assessments of adverse events and remission status due to reference ranges based on ANC levels of individuals without BEN/DANC. The lack of awareness and the time required to evaluate the cause of neutropenia can disrupt lifesaving treatments.

A solution exists through the prompt clarification of BEN/DANC status during the initial cancer evaluation. The newly designed algorithm (Figure 3) will aid oncology advanced practitioners (APs) in preventing therapy disruptions and foster a population-based, patient-centered approach for

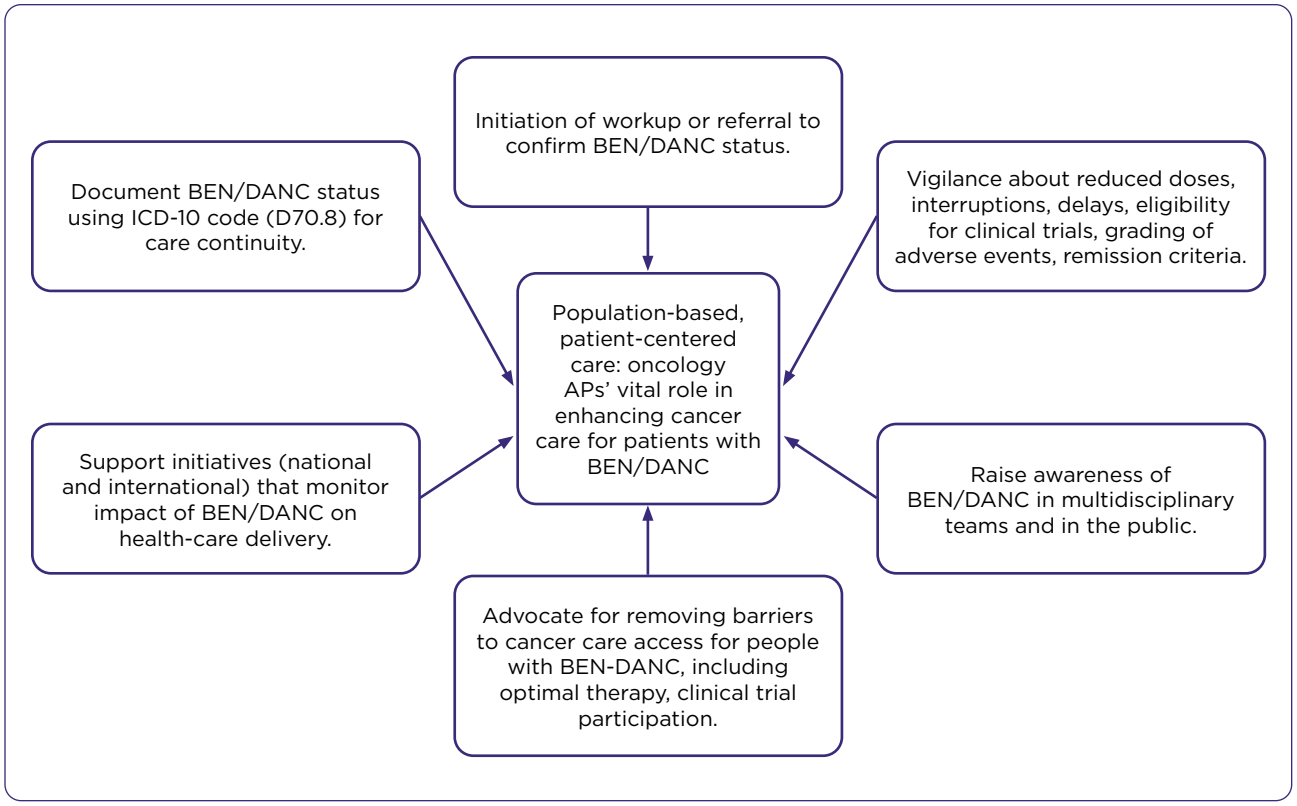

Figure 4. Population-based, patient-centered care: Oncology advanced practitioners' vital role in enhancing cancer care for patients with BEN/DANC.

cancer patients with BEN/DANC. Oncology APs, who are at the forefront of practice changes, can incorporate the use of the algorithm in Figure 3 into their practice. When combined with the actions outlined in Figure 4, this approach will enhance oncology care for patients with BEN/DANC. It is cost-effective, timesaving, and therapy-optimizing to clarify cancer patients' BEN/DANC status. Oncology APs are gaining a tool that facilitates the prevention of therapy disruptions for certain patients with cancer. ●

Disclosure

The author has no conflict of interest to disclose.

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