Gene test interpretation: *ACKR1* (Duffy blood group gene)

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INTRODUCTION

The *ACKR1* gene encodes the Duffy antigen receptor for chemokines (DARC), which is expressed on red blood cells (RBCs), endothelial cells, and other cell types.

Genetic variation in *ACKR1* determines Duffy blood group status, which in turn impacts malaria resistance, hemolytic transfusion reactions, and hemolytic disease of the fetus and newborn (HDFN). Duffy antigen expression also affects baseline neutrophil counts.

Testing of *ACKR1* may be performed as a component of a multi-gene panel for transfusion antigens ("RBC genotyping") to guide transfusions and evaluate hemolytic transfusion reactions. Targeted testing of *ACKR1*, especially for the c.-67T>C variant, may be performed to identify a genetic influence on baseline neutrophil counts. (See 'Neutrophils (effect of Duffy status)' below.)

This monograph discusses clinical implications of *ACKR1* variants. Details of indications for testing and management are discussed separately [1]. (See 'UpToDate topics' below.)

BACKGROUND

Terminology

- ***ACKR1* and DARC** – *ACKR1* (figure 1) encodes the atypical chemokine receptor 1, also called Duffy antigen receptor for chemokines (DARC). *DARC* was the former name of the

ACKR1 gene.

The DARC protein is a transmembrane receptor for chemoattractant cytokines (chemokines) of the CXC and CC families. (See "Transplantation immunobiology", section on 'Chemokines and chemokine receptors'.)

Other names for the protein include Duffy blood group, Fy glycoprotein, and CD234.

- **Duffy blood group antigens** – Duffy (Fy) blood group antigens (Fy^a and Fy^b) are genetically determined by a single nucleotide difference in the *ACKR1* coding region that changes a single amino acid.
  - Fy^a – Guanine at nucleotide 125 defines the *FY*A* haplotype, with glycine at amino acid 42.
  - Fy^b – Adenine at nucleotide 125 defines *FY*B* haplotype, with aspartate at amino acid 42.
- **Duffy-null phenotype** – Duffy-null, also called Fy(a−b−), is characterized by lack of Duffy antigens on red blood cells (RBCs). (See "Red blood cell antigens and antibodies", section on 'Duffy antigens'.).

  The Duffy-null phenotype is caused by a variant in the *ACKR1* promoter that results in loss of expression of Duffy antigens on RBCs but does not affect expression on other cell types. (See 'Expression of ACKR1/DARC' below.)
- **DANC** – Duffy-null associated neutrophil count (DANC) is the normal range for neutrophil counts in individuals with Duffy-null RBCs. This is a genetically-determined baseline neutrophil count that is often lower than commonly-used laboratory reference ranges. This was formerly known as "**benign ethnic neutropenia**," but it is not a form of neutropenia or a risk factor for infection; rather, DANC represents normal human variation. (See 'Reference ranges for Duffy-null and non-Duffy-null' below.)

Expression of *ACKR1*/DARC

- **RBCs**
  - **Duffy blood group** – The variants that determine Fy^a and Fy^b are autosomal co-dominant. (See "Red blood cell antigens and antibodies", section on 'Duffy antigens'.)

    Presence of the variant at one allele is sufficient to confer the presence of that Duffy antigen. There are four main RBC phenotypes:

    - Fy(a+b+)

- Fy(a+b−)
- Fy(a−b+)
- Fy(a−b−), also called Duffy-null

- **Duffy-null** – The presence or absence of Duffy antigens on RBCs depends on erythroid-specific transcription of *ACKR1*. Absence of Duffy antigens (Duffy-null) results from homozygosity for the *ACKR1* promotor variant rs2814778-C, which contains cytosine instead of thymine at position –67 (also designated –46, depending on the numbering system), which prevents binding of the GATA1 transcription factor (figure 1) in RBC precursors [2]. The variant is designated c.-67T>C; homozygosity may be abbreviated C/C.

  The c.-67T>C promoter variant is commonly linked to the coding region variant *FY*B* [3]. It prevents expression of the *FY*B* allele and is sometimes called $FY*B^{ES}$ for "erythrocyte silent." The variant can rarely be associated with *FY*A* ($FY*A^{ES}$).

  Duffy-null status is autosomal recessive. Only individuals who are homozygous for the c.-67T>C variant are Duffy-null. Other rare *ACKR1* variants can also cause the Duffy-null phenotype but do not affect neutrophil count [2].

- **Neutrophils** – DARC (and Duffy antigens) are not expressed on neutrophils. However, the presence or absence of Duffy antigens on RBCs affects the baseline neutrophil count. (See 'Neutrophils (effect of Duffy status)' below.)

- **Endothelial and epithelial cells** – DARC is expressed on endothelial cells (capillary and postcapillary venules), epithelial cells (kidneys, collecting ducts, and lung alveoli), and Purkinje cells in the cerebellum.

  Homozygosity for c.-67T>C does not affect expression *of FY*B* in non-RBC cell types. This is why Duffy-null individuals generally do not develop anti-Fy^b [2].

Geographic variation — Geographic mapping has been used to determine the distribution of *ACKR1* alleles. The most common alleles in contemporary populations are [3]:

- **Sub-Saharan Africa** – $FY*B^{ES}/FY*B^{ES}$ (producing the Duffy-null phenotype) in >95 percent
- **Americas** – *FY*A/FY*B* in 31 percent
- **Europe** – *FY*A/FY*B* in 52 percent
- **Asia** – *FY*A/FY*A* in >80 percent

Worldwide distribution of the Duffy-null phenotype is illustrated in the figure (figure 2).

CLINICAL IMPLICATIONS

How to read the genetic test report — As with all genetic testing, confirm the correct person was tested, determine which gene(s) were evaluated, and verify that the test was performed in a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory or other nationally certified laboratory. These principles are summarized in the table (table 1).

Duffy blood group antigens — All red blood cells (RBCs) have surface antigens that determine blood type. When certain antigens are absent, exposure to these antigens via allogeneic blood (transfusion, pregnancy, sharing needles) can elicit an immune response. Alloantibodies against Duffy blood group antigens (anti-Fy) can cause clinically significant hemolysis (table 2).

Genetic testing and RBC serologic testing are considered comparable for determining Duffy antigen status for transfusion practice. Most transfusion medicine services will use serologic testing, although the genotype may be helpful in certain settings such as recent transfusion.

Hemolytic transfusion reactions — Hemolytic transfusion reactions can occur when an individual has an alloantibody against Fy^a or Fy^b and is transfused with RBCs that express that antigen. (See "Hemolytic transfusion reactions", section on 'Pathophysiology'.)

- Individuals who are Fy(a+b–) can make anti-Fy^b.
- Individuals who are Fy(a-b+) can make anti-Fy^a.
- Individuals who are Fy(a+b+) do not make anti-Fy^a or anti-Fy^b.
- Individuals who are Duffy-null typically can make anti-Fy^a but not anti-Fy^b, because they express the "b" antigen on other tissues. (See 'Expression of ACKR1/DARC' above.)

Routine pretransfusion testing will identify alloantibodies to Duffy antigens. If transfusion is needed, antigen-negative units will be provided. (See "Pretransfusion testing for red blood cell transfusion", section on 'Antibody screen'.)

Hemolytic disease of the fetus and newborn (HDFN) — If fetal RBCs express antigens inherited from the father that are recognized by the maternal immune system as foreign, alloimmunization can occur, and alloantibodies can cross the placenta and cause hemolysis in the fetus and newborn.

Anti-Fy^a can be associated with HDFN. During pregnancy, a maternal antibody screen that identifies anti-Fy^a will prompt testing of the father and enhanced monitoring for HDFN if appropriate. (See "Management of non-RhD red blood cell alloantibodies during pregnancy", section on 'Duffy' and "Management of non-RhD red blood cell alloantibodies during pregnancy", section on 'Antibody screening'.)

Malaria risk — Duffy antigen receptor for chemokines (DARC) serves as the only receptor on RBCs for *Plasmodium vivax* and the less common *P. knowlesi* [3]. Duffy-null individuals are

protected from infection with these malarial species. *P vivax* and *P knowlesi* merozoites can attach to Fy(a–/b–) RBCs, but they cannot enter the RBC and eventually detach, leaving the cell markedly deformed. Risk for other malaria species is not affected. (See "Pathogenesis of malaria" and "Protection against malaria by variants in red blood cell (RBC) genes", section on 'Duffy blood group system'.)

Neutrophils (effect of Duffy status)

Absolute neutrophil count (ANC) — An individual's Duffy status (Duffy-null versus non-Duffy-null) affects the reference ranges for baseline neutrophil counts. Duffy-null status is a normal variant. It is not a disease, and it does not cause any clinical disorder (table 2).

The ANC is an absolute number of mature neutrophils and band forms per unit of blood and thus a more accurate measure of the quantity of circulating neutrophils than the percentage of neutrophils.

The mechanism by which Duffy status determines the normal range for the ANC remains unclear. Hypotheses include a role for RBC DARC as a sink for circulating chemokines, alterations in precursor cell differentiation in the bone marrow, and increased trafficking of neutrophils to other compartments (spleen, bone marrow, vasculature, or other tissues) in Duffy-null individuals [2,4,5]. DARC is not expressed on neutrophils. (See 'Expression of ACKR1/DARC' above.)

Reference ranges for Duffy-null and non-Duffy-null — Reference ranges for ANC differ for individuals with Duffy-null and non-Duffy-null phenotypes (reference ranges also differ for children and adults). Duffy-null-associated neutrophil count (DANC) refers to the ANC in individuals who are homozygous for the c.-67T>C promotor variant in *ACKR1*. (See 'Expression of ACKR1/DARC' above.)

If there is a question regarding the reference range for a particular individual, Duffy-null status can be ascertained by genotyping (preferred) or by RBC phenotyping using serologic testing. Serologic RBC phenotyping may have an important limitation in identifying DANC, as RBCs may type as Duffy-null if they are Fy(a–b–) or if they carry the rare variant Fy^x, which is not associated with DANC [6].

Geographic ancestry may be a reasonable marker of increased likelihood of a certain genotype (see 'Geographic variation' above), but race should not be used as a proxy for biological differences in neutrophil count [7,8]. (See "Overview of neutropenia in children and adolescents", section on 'Normal variants' and "Approach to the adult with unexplained neutropenia", section on 'Normal variants <1500/microL'.)

In a study of 120 individuals who self-identified as Black or African American seen for routine, nonurgent outpatient visits, 80 (67 percent) were Duffy-null and 40 (33 percent) were

non-Duffy-null [9]. ANCs in the two groups were:

- **Duffy-null** – Median ANC 2820/microL, range 1080 to 5950/microL
- **Non-Duffy-null** – Median ANC 5005/microL, range 2360 to 10,500/microL

Nearly one-fourth of Duffy-null individuals had an ANC below the lower limit of published reference intervals; one-tenth had an ANC <1500/microL, which despite being a normal variant in these participants could be designated as neutropenia and could lead to unnecessary bone marrow examinations and inappropriate dose reduction or withholding of important medications. (See 'Drug dosing' below.)

A larger study reported similar findings, with an ANC <1000/microL in >5 percent of individuals with DANC [10].

Risk of infections — DARC has no impact on response to bacterial or common viral infections [11]. People with DANC have normal bone marrow cellularity and a robust neutrophil response to infection [9].

- Duffy-null individuals have resistance to *P vivax* and *P knowlesi* malaria. (See 'Malaria risk' above.)

- Some studies have suggested that Duffy-null individuals have an increased risk of HIV infection; others have suggested they have a survival advantage with HIV [2,12].

Drug dosing — One concern for individuals with DANC is that they will receive dose reductions or have doses held for important drugs based on their lower baseline neutrophil count; this may include critical medications for inflammatory conditions, sickle cell disease, and cancer.

It is important to consider the possibility of DANC and to avoid inadvertently withholding or underdosing medications, a practice that affects predominantly people with African ancestry [13]. Genotyping or phenotyping for DANC can reduce racial disparities in health care. (See "Overview of pharmacogenomics", section on 'Potential benefits of genotyping'.)

First-degree relatives — First-degree relatives of the tested individual may benefit from knowing their *ACKR1* genotype or Duffy antigen status for purposes of determining whether their ANC is in the normal range and in determining the likelihood of HDFN during pregnancy. (See 'Clinical implications' above.)

Consultation with experts in genetics, hematology, or transfusion medicine may be helpful. (See 'Listings of experts' below.)

RESOURCES

UpToDate topics

- **Duffy antigen –** (See "Red blood cell antigens and antibodies", section on 'Duffy blood group system'.)
- **Neutrophil count –** (See "Overview of neutropenia in children and adolescents" and "Approach to the adult with unexplained neutropenia".)
- **Transfusion reactions –** (See "Hemolytic transfusion reactions".)
- **Hemolytic disease of the fetus and newborn –** (See "Management of non-RhD red blood cell alloantibodies during pregnancy".)

Listings of experts

- **Genetic counselors –** National Society of Genetic Counselors (NSGC)
- **Clinical geneticists –** American College of Medical Genetics and Genomics (ACMG)
- **Hematologists –** American Society of Hematology (ASH)
- **Transfusion medicine –** Association for the Advancement of Blood & Biotherapies (AABB)

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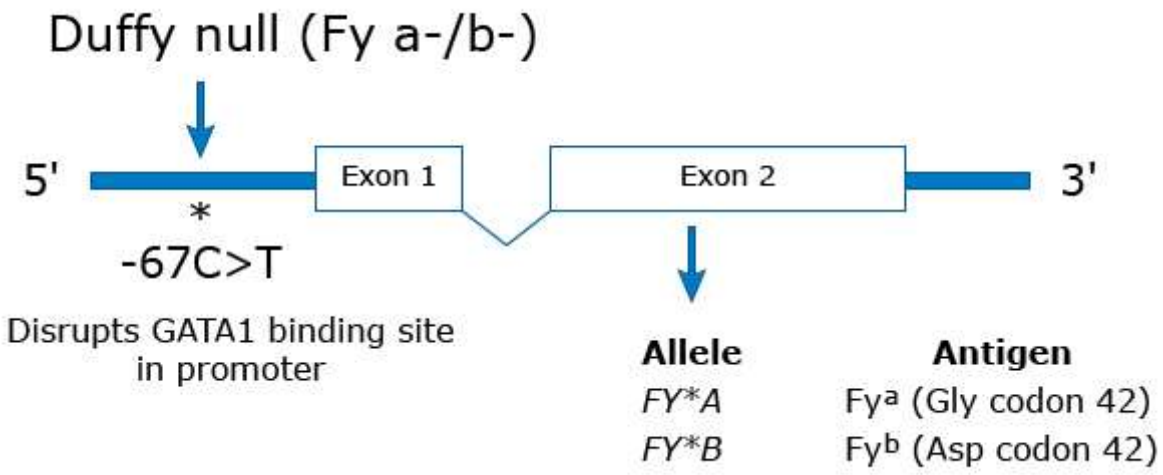
Topic 139725 Version 4.0

GRAPHICS

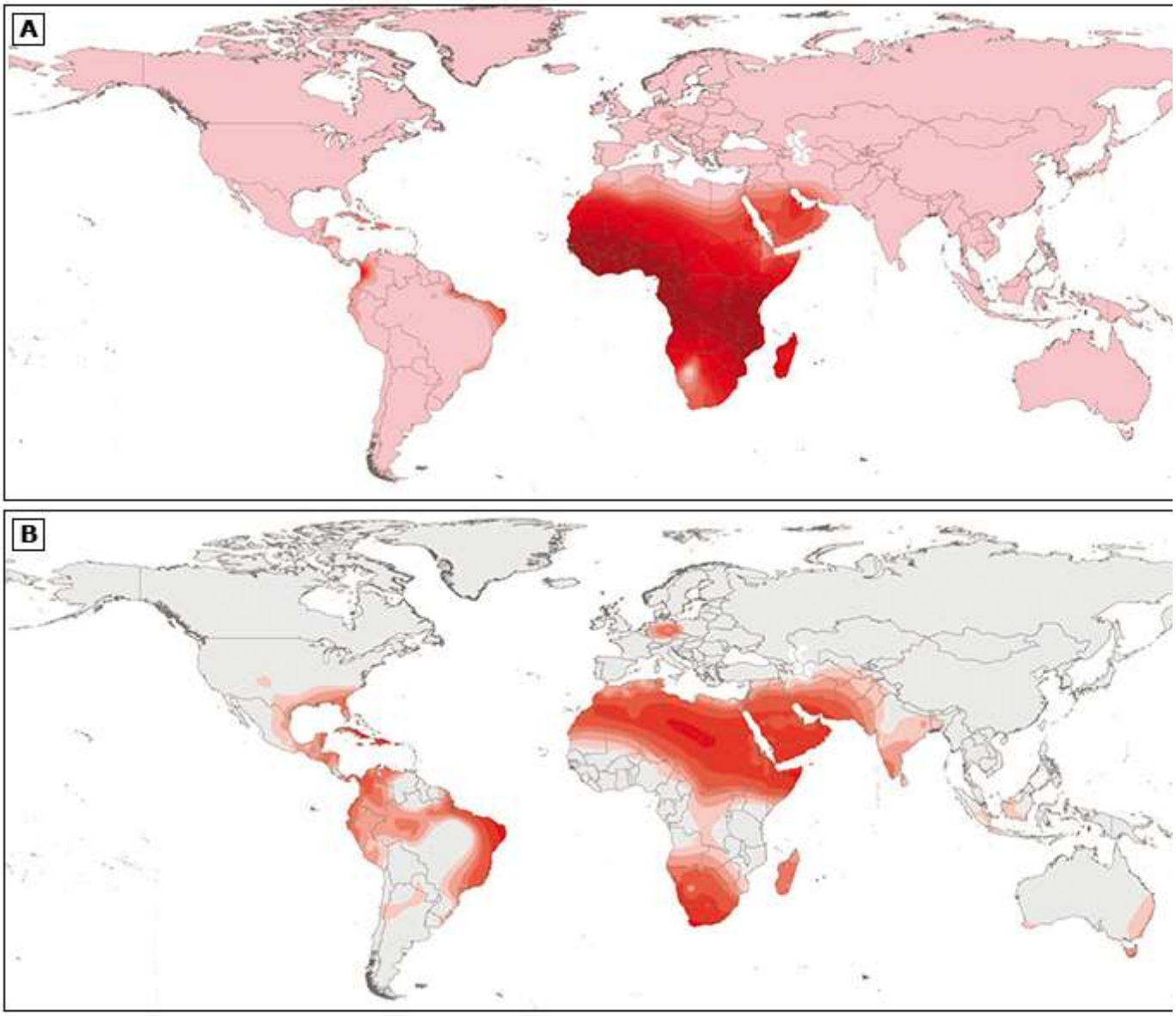
ACKR1 gene



Schematic presentation of the *ACKR1* gene, which encodes the atypical chemokine receptor 1, also called Duffy antigen receptor for chemokines (DARC). There are two Duffy alleles (*FY*A* and *FY*B*), which encode for the two Duffy blood group antigens (Fy^a and Fy^b); they differ by a single amino acid at codon 42. The polymorphism in the promoter (–67C>T) results in loss of gene expression and produces the erythroid Duffy-null (Fy a–/b–) phenotype.

Graphic 140094 Version 1.0

Global distribution of the Duffy-null phenotype



(A) Heat map showing the global prevalence of the Duffy-null phenotype, characterized by lack of Duffy a
Fy(a–b–).

(B) Corresponding uncertainty map (interval between the 25% and 75% quartiles of the posterior distribu

RBCs: red blood cells; IQR: interquartile range.

Graphic 141360 Version 1.0

Checklist for reviewing the accuracy and interpretation of genetic test results

Section of the report	Action(s)	Concern(s)
Patient identification	▪ Verify the patient identification with at least two independent identifiers. ▪ Repeat testing if clinically indicated* and the original testing does not have a proper "chain of evidence."	▪ Individuals may inadvertently provide the wrong name or date of birth on a test sample. ▪ Testing should be done by a laboratory that can ensure that the identification matches the tested individual.
Testing laboratory	▪ Verify that testing was done in a CLIA-certified laboratory (or other nationally certified laboratory). ▪ Repeat testing if clinically indicated and/or if original results are actionable and testing was not performed in a CLIA or other nationally certified laboratory.	▪ All actionable medical testing (eg, positive finding or negative finding in an individual suspected of having a genetic disorder) should be conducted in a CLIA-certified laboratory (or other nationally certified laboratory) that has met appropriate quality standards for performing the specific test. ▪ In the United States, most certification is performed by the College of American Pathologists (CAP) and a CAP number for the laboratory is listed. ▪ Some direct-to-consumer testing in some countries is not performed in certified laboratories and may lack appropriate quality controls.
Date of testing	▪ Review the testing date. ▪ Request reinterpretation of the results if the interpretation is inconclusive (eg, a variant of uncertain significance [VUS]).	▪ Germline variants do not change over time. However, as new data become available, the classification of variant pathogenicity may change, especially for variants classified as variant of uncertain significance (VUS). ▪ Repeat testing may be considered, as the technologies for exome sequencing may improve and may identify a variant missed on a prior test.
Gene(s) tested	▪ Verify which genes were tested. ▪ If testing was performed to evaluate a medical condition or a familial disorder, ensure	▪ Not all genetic testing panels are comprehensive for the genes that can cause a particular health condition or for the variants in those genes that the panel evaluates.

	that the correct gene(s), and variant(s), if applicable, were included. ▪ If new research has identified new disease genes, additional testing may be appropriate.	▪ New disease genes or clinically important variants in existing genes may be identified through further research.
Testing method	▪ Review whether the gene(s) were evaluated using genome sequencing, exome sequencing, panel testing, or other methods such as Sanger sequencing for a specific variant.	▪ Not all methods will identify all variants. ▪ In some cases such as *HFE* testing, only one or two variants are clinically relevant, and sequencing of the entire coding region of the gene is not required, whereas in other conditions, limited testing for one or two variants may miss clinically important findings. ▪ Gene panels may be especially useful when multiple genes could potentially be responsible for a clinical phenotype.
Classification of pathogenicity	▪ Review the category of pathogenicity that was assigned to each variant. ▪ For a variant of uncertain significance (VUS; or any variant for which interpretation is inconclusive), consider requesting reinterpretation annually and/or before making a final decision on interventions.	Interpretation of pathogenicity incorporates many data sources including laboratory research, research databases, population studies, and pedigree analyses. ▪ In some cases, pathogenicity is well established (eg, the known variant that causes sickle cell disease); in others, it is more subjective and incomplete. The designation of a variant of uncertain significance (VUS) refers to the lack of available information on pathogenicity for the variant; further information may eventually allow pathogenicity to be determined. ▪ Variants of uncertain significance (VUS), likely benign, or benign are generally not considered actionable and should not impact medical interventions, which would typically be based on personal and family history of disease. ▪ Consulting a publicly curated database such as ClinVar (or other disease-specific specialty database), discussing the results with an expert in the specific disease, or referral to a clinical geneticist, genetic counselor, or disease expert may be helpful.

Clinicians should view the report themselves and should not make clinical decisions based on a verbal report or written summary of the results. Refer to UpToDate for additional information about genetic testing. Details of variant nomenclature (DNA and protein) are available from the Human Genome Variation Society (HGVS) at https://varnomen.hgvs.org/.

CLIA: Clinical Laboratory Improvement Amendments (the national certification standard in the United States); PCR: polymerase chain reaction.

* Indications for testing vary according to the individual's medical history, family history, and other factors such as desire for preconception counseling. In some cases, an individual who did not have a clinical indication for testing may have an unexpected finding from genetic testing that, if accurate, would indicate the need for an intervention, and such findings may be actionable regardless of the initial reasons for testing.

Graphic 122437 Version 10.0

Implications of *ACKR1* genotype and Duffy status

	***ACKR1* genotype/Duffy phenotype**	
	Duffy-null*	**Non-Duffy-null**
Hemolytic transfusion reactions (HTRs)¶	▪ Alloimmunization and HTRs can occur if non-Duffy-null blood is transfused (mostly applies to Fy^a positive).	▪ Alloimmunization and HTRs can occur if Fy^a positive RBCs are transfused to a recipient who is Fy^a negative. ▪ Alloimmunization and HTRs can occur if Fy^b positive RBCs are transfused to a recipient who is Fy^b negative.
Hemolytic disease of the fetus and newborn (HDFN)Δ	▪ HDFN can occur if the mother is Fy^a negative and the father is Fy^a positive.	▪ HDFN can occur if father expresses Fy^a and mother is Fy^a negative.
ANC normal range	▪ Lower ANC range than non-Duffy-null.	▪ Higher ANC range than Duffy-null.
Risk of infections	▪ No increased risk of bacterial infections. ▪ Protection from *P. vivax* and *P. knowlesi* malaria. ▪ Possible altered risk or disease course for HIV compared with non-Duffy-null individuals.	▪ No increased risk of bacterial infections. ▪ No protection from *P. vivax* and *P. knowlesi* malaria. ▪ Possible altered risk or disease course for HIV compared with Duffy-null individuals.
Drug dosing	Drug dosing should not be altered based on baseline ANC (consider Duffy-null specific reference ranges).	
Relatives	May benefit from knowing their status for reasons mentioned above.	

Information about *ACKR1* genotype or Duffy phenotype may help individuals understand their risk of transfusion reactions and HDFN, but serologic testing is the gold standard. Information about normal neutrophil ranges can help individuals avoid unnecessary evaluations and can avoid inadvertent withholding or under-dosing medications that affect the neutrophil count, a practice that affects predominantly people with African ancestry. For identifying Duffy-null status, serologic testing for Fy^a and Fy^b or genetic testing of *ACKR1* can be used. Genetic testing is especially helpful if serologic typing results are inconsistent with the antibody screen or if the patient has been recently transfused.

ACKR1: atypical chemokine receptor 1; HTR: hemolytic transfusion reaction; RBC: red blood cell; HDFN: hemolytic disease of the fetus and newborn; Fy: Duffy antigen; ANC: absolute neutrophil

count.

* Other designations for Duffy-null include:
    - c.-67 C/C
    - Homozygous c.-67T>C
    - Homozygous rs2814778-C
    - FY*B^{ES}/*B^{ES}
    - Fy(a–b–)

¶ Pretransfusion testing is routinely used to avoid antigens implicated in hemolytic transfusion reactions.

Δ Maternal antibody screen is routinely performed during pregnancy to identify risk for HDFN and need for additional testing and monitoring. Only anti-Fy^{a} has been associated with HDFN.

Contributor Disclosures

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