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Clinician Management Resource for *DDX41*

This overview of clinical management guidelines is based on this patient's positive test result for a pathogenic or likely pathogenic *DDX41* variant. Unless otherwise stated, medical management guidelines used here are limited to those published in the Recommendations from the Nordic MDS Study Group since U.S. consensus practice guidelines have not been developed. Please consult the referenced guideline for complete details and further information.

Clinical correlation with the patient's past medical history, treatments, surgeries, and family history may lead to changes in clinical management decisions; therefore, other management recommendations may be considered. Genetic testing results and published guidelines help inform medical management decisions but do not constitute formal recommendations. Discussions of medical management decisions and individualized treatment plans should be made in consultation between each patient and his or her healthcare provider and may change.

SCREENING/SURGICAL CONSIDERATIONS[1]	INITIAL WORKUP	FOLLOW-UP Beginning at age 50 years or earlier, if indicated (cytopenia and/or clonal abnormalities)
Myelodysplastic syndrome (MDS) and Acute Myeloid Leukemia (AML)		
Complete blood count (CBC) and clinical assessment*	Following identification of an LP/P *DDX41* variant	Every 12 months if previously normal CBC
Bone marrow aspirate/biopsy with cytogenetic analysis	Following identification of an LP/P *DDX41* variant, only in the presence of aberrant CBC or previously identified somatic variants (clonal hematopoiesis)	Follow-up if progression is suspected from CBC/clinical assessment/NGS results
Next generation sequencing panel of recurrently mutated genes in myeloid neoplasm (including *DDX41*)	Following identification of an LP/P *DDX41* variant (bone marrow or blood samples in case of aberrant or normal CBC, respectively)	Every second year (blood) if no signs of progression are detected
Management and surveillance		
Referral to a hematology clinic with expertise in the management of patients with germline predisposition to hematological neoplasms	Following identification of an LP/P *DDX41* variant	N/A
Other		
Referral to genetic counseling	Following identification of an LP/P *DDX41* variant	N/A
Encourage participation in registries and/or academic studies investigating further the role of *DDX41* in hematological diseases	Individualized	Individualized
The risk classification of myeloid neoplasm and the decision to perform an allo-HSCT in patients with a germline *DDX41* variant should be based on the diagnosis-specific guidelines**	Individualized	Individualized

* Clinical assessment should include investigation for signs and symptoms of MDS/AML/other malignancies.

** According to current knowledge, the presence of an LP/P germline *DDX41* variant is not considered an indication for allo-HSCT. Recent retrospective studies in cohorts of DDX41-mutated AML or MDS showed no significant survival benefit in patients who underwent allo-HSCT.

1. Baliakas P, et al. (2024) *HemaSphere* **8**(8):e145. https://pubmed.ncbi.nlm.nih.gov/39139355/

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Understanding Your Positive *DDX41* Genetic Test Result

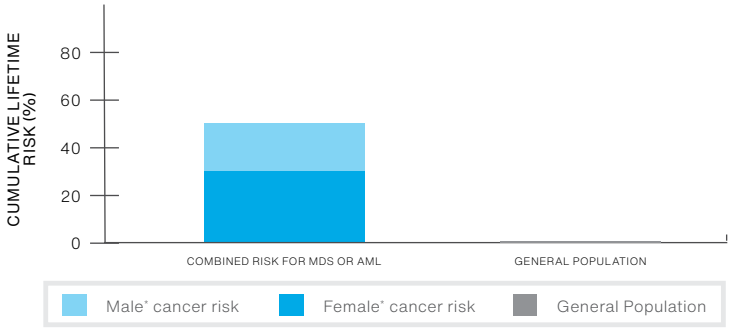
INFORMATION FOR PATIENTS WITH A PATHOGENIC OR LIKELY PATHOGENIC VARIANT

5 Things To Know

1	Result	Your testing shows that you have a pathogenic or likely pathogenic variant in the *DDX41* gene. A pathogenic or likely pathogenic *DDX41* variant may be in a person's body from birth (germline), or may have occurred at some point during a person's lifetime (somatic).
2	*DDX41*-related hematologic malignancy predisposition syndrome	People with germline pathogenic or likely pathogenic *DDX41* variants have *DDX41*-related hematologic malignancy predisposition syndrome.
3	Cancer risks	People with germline pathogenic or likely pathogenic *DDX41* variants are at increased risk for certain blood disorders and cancers including myelodysplatic syndrome (MDS) and acute myelogenous leukemia (AML). Some people with germline pathogenic or likely pathogenic *DDX41* variants may develop other types of blood disorders or cancers such as multiple myeloma, chronic myeloid leukemia (CML), lymphoma, or bone marrow failure (aplastic anemia). These conditions usually occur later in life, after 60 years. Somatic pathogenic or likely pathogenic *DDX41* variants do not run in families and cannot be passed on to children; however, they may occur because of an active blood disorder such as leukemia. It is important to discuss your result in detail with your healthcare provider.
4	What you can do	Risk management decisions are very personal. There are options to detect cancer early or lower the risk to develop cancer. It is important to discuss these options with your healthcare provider and decide on a plan that works for you.
5	Family	Family members may also be at risk – they can be tested for the pathogenic or likely pathogenic *DDX41* variant that was found in you. It is recommended that you share this information with your family members so they can learn more and discuss with their healthcare providers.

DDX41 Lifetime Cancer Risks**

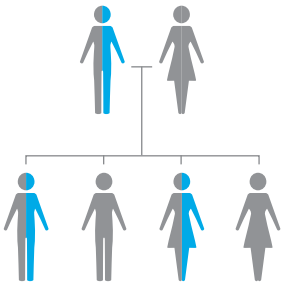
For people with germline pathogenic or likely pathogenic variants



* Refers to sex assigned at birth.
** Because risk estimates vary in different studies, only approximate risks are given. Cancer risks will differ based on individual and family history.

DDX41 in the Family

There is a 50/50 random chance to pass on a germline pathogenic or likely pathogenic *DDX41* variant to each of your children.



- Has a germline pathogenic or likely pathogenic *DDX41* variant
- No germline pathogenic or likely pathogenic *DDX41* variants

RESOURCES

- American Cancer Society cancer.org
- Genetic Alliance geneticalliance.org
- National Organization for Rare Diseases (NORD) rarediseases.org
- National Society of Genetic Counselors nsgc.org
- Canadian Society of Genetic Counsellors cagc-accg.ca

Please discuss this information with your healthcare provider. The cancer genetics field is continuously evolving, so updates related to your *DDX41* result, medical recommendations, and/or potential treatments may be available over time. This information is not meant to replace a discussion with a healthcare provider, and should not be considered or interpreted as medical advice.

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