GENETIC TESTING FOR FLT3, NPM1 AND CEBPA VARIANTS IN CYTOGENETICALLY NORMAL ACUTE MYELOID LEUKEMIA

Non-Discrimination Statement and Multi-Language Interpreter Services information are located at the end of this document.

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Medical Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Medical Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as “Description” defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as “Criteria” defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Medical Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Medical Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.

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GENETIC TESTING FOR FLT3, NPM1 AND CEBPA VARIANTS IN CYTOGENETICALLY NORMAL ACUTE MYELOID LEUKEMIA (cont.)

Description:

Treatment of acute myeloid leukemia (AML) is based upon risk stratification, mainly individual age and tumor cytogenetics (karyotyping) which allow for individuals to be divided into good, intermediate and poor risk categories. Three of the most frequent molecular changes with prognostic impact are variants of CEBPA encoding a transcription factor, variants of the FLT3 gene, encoding a receptor of tyrosine kinase involved in hematopoiesis and variant of the NPM1 gene, encoding a shuttle protein within the nucleolus. The identification of these variants has been investigated in the management of this disease.

CEBPA Variants:
CEBPA (CCAAT/enhancer binding protein) is a transcription-factor gene which plays a role in cell cycle regulation and cell differentiation. Variants to CEBPA are found in approximately 15% of individuals with AML with a normal karyotype. CEBPA variants can be either biallelic (double variants) or monoallelic. Monoallelic variants are prognostically similar to CEBPA wild type and do not confer a favorable prognosis in cytogenetically normal AML; double variants of CEBPA have shown a better prognosis with higher rates of CR and OS after standard induction chemotherapy.

FLT3 Variants:
FMS-like tyrosine kinase (FLT3) plays a critical role in normal production and cellular growth in hematopoietic stem and progenitor cells. Variants in FLT3 are one of the most frequently encountered variants in AML, and approximately 30% of individuals with AML harbor some form of FLT3 variant. FLT3 variants are divided into two categories:

- Internal tandem duplications (FLT3-ITD) variants: occur in or near the juxtamembrane domain of the receptor
- Point variants resulting in single amino acid substitutions within the activation loop of the tyrosine kinase domain (FLT3-TKD)

FLT3-ITD variants are much more common than FLT3-TKD variants. The LeukoStrat® CDx FLT3 Mutation Assay is a PCR-based in vitro diagnostic test designed to detect FLT3-ITD and FLT3-TKD variants in genomic DNA extracted from mononuclear cells obtained from peripheral blood or bone marrow aspirates of individuals diagnosed with acute myelogenous leukemia. The LeukoStrat CDx FLT3 Mutation Assay is used as an aid in the assessment of individuals for whom oral midostaurin treatment is being considered.
GENETIC TESTING FOR FLT3, NPM1 AND CEBPA VARIANTS IN CYTOGENETICALLY NORMAL ACUTE MYELOID LEUKEMIA (cont.)

Description: (cont.)

NPM1 Variant:
The most common molecular abnormality in AML is a variant of NPM1, which is found in 46-64% of cytogenetically normal AML (CN-AML) and 9-18% of cytogenetically abnormal AML. Up to 50% of AML with mutated NPM1 also carry a FLT3-ITD. Individuals with CN-AML with either the presence or absence of a FLT3-ITD have a more favorable prognosis.

Definitions:

Genetic Testing:
Analysis of DNA, RNA, chromosomes, proteins and certain metabolites in order to detect alterations related to an inherited disorder.

Gene:
A hereditary unit consisting of segments of DNA that occupies a specific location on chromosomes. Genes undergo mutation when their DNA sequence changes.

Genetic Counseling:
Instruction that provides interpretation of genetic tests and information about courses of action that are available for the care of an individual with a genetic disorder or for future family planning.

Affected Individual:
An individual displaying signs or symptoms characteristic of a suspected or specific inherited disorder.

Unaffected Individual:
An individual who displays no signs or symptoms characteristic of a suspected or specific inherited disorder.

Screening:
Genetic screening is the testing of an individual with no symptoms for a specific inherited disorder to determine if the individual carries an abnormal gene. Screening can be used to predict risk or potential risk for the individual or their offspring.
GENETIC TESTING FOR FLT3, NPM1 AND CEBPA VARIANTS IN CYTOGENETICALLY NORMAL ACUTE MYELOID LEUKEMIA (cont.)

Criteria:

For oral medication Rydapt (midostaurin), see applicable BCBSAZ Pharmacy Coverage Guidelines.

- Genetic testing and/or counseling of an unaffected individual, regardless of risk factors is considered screening and not eligible for coverage.

- Genetic testing and/or counseling of an affected individual to confirm a disease when confirmation of the diagnosis would not impact the care and/or management is considered not medically necessary and not eligible for coverage.

- Genetic testing for FLT3, NPM1 and CEBPA variants is considered medically necessary in cytogenetically normal AML.

- Genetic testing with the LeukoStrat CDx FLT3 Mutation Assay to detect variants in FLT3 is considered medically necessary with documentation of ALL of the following:
  1. Individual has a diagnosis of acute myelogenous leukemia (AML)
  2. Individual is being considered for treatment with midostaurin and ONE of the following:
     - Induction therapy in combination with standard cytarabine and daunorubicin
     - Consolidation therapy in combination with cytarabine
     - Single agent therapy after consolidation therapy

- Genetic testing for FLT3, NPM1 and CEBPA variants for all other indications not previously listed or if above criteria not met is considered experimental or investigational based upon:
  1. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes, and
  2. Insufficient evidence to support improvement of the net health outcome, and
  3. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives, and
  4. Insufficient evidence to support improvement outside the investigational setting.

These indications include, but are not limited to:

- To detect minimal residual disease
GENETIC TESTING FOR FLT3, NPM1 AND CEBPA VARIANTS IN CYTOGENETICALLY NORMAL ACUTE MYELOID LEUKEMIA (cont.)

Resources:

Literature reviewed 02/20/18. We do not include marketing materials, poster boards and non-published literature in our review.

The BCBS Association Medical Policy Reference Manual (MPRM) policy is included in our guideline review. References cited in the MPRM policy are not duplicated on this guideline.


GENETIC TESTING FOR FLT3, NPM1 AND CEBPA VARIANTS IN CYTOGENETICALLY NORMAL ACUTE MYELOID LEUKEMIA (cont.)

Non-Discrimination Statement:

Blue Cross Blue Shield of Arizona (BCBSAZ) complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability or sex. BCBSAZ provides appropriate free aids and services, such as qualified interpreters and written information in other formats, to people with disabilities to communicate effectively with us. BCBSAZ also provides free language services to people whose primary language is not English, such as qualified interpreters and information written in other languages. If you need these services, call (602) 864-4884 for Spanish and (877) 475-4799 for all other languages and other aids and services.

If you believe that BCBSAZ has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability or sex, you can file a grievance with: BCBSAZ’s Civil Rights Coordinator, Attn: Civil Rights Coordinator, Blue Cross Blue Shield of Arizona, P.O. Box 13466, Phoenix, AZ 85002-2466, (602) 864-2288, TTY/TDD (602) 864-4823, crc@azblue.com. You can file a grievance in person or by mail or email. If you need help filing a grievance BCBSAZ’s Civil Rights Coordinator is available to help you. You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at: U.S. Department of Health and Human Services, 200 Independence Avenue SW., Room 509F, HHH Building, Washington, DC 20201, 1–800–368–1019, 800–537–7697 (TDD). Complaint forms are available at http://www.hhs.gov/ocr/office/file/index.html

Multi-Language Interpreter Services:

Spanish: Si usted, o alguien a quien usted está ayudando, tiene preguntas acerca de Blue Cross Blue Shield of Arizona, tiene derecho a obtener ayuda e información en su idioma sin costo alguno. Para hablar con un intérprete, llame al 602-864-4884.

Navajo: Díí kweé átah nílínígíí Blue Cross Blue Shield of Arizona haada ylt‘éego bíná’idílíkidgo ée doodago Háida bíjá aniyeedíígí t‘áadoo le’é yína’idílíkidgo bee haz‘ánii hólo díí t‘áa hazaad’ehí háhá a’doowolgo bee haz‘a doo bááh ilínígoó. Aта’ halne‘ígíí koj’ bíchí’j’ hodilíníí 877-475-4799.

Chinese: 如果您，或是您正在協助的對象，有關於插入項目的名稱 Blue Cross Blue Shield of Arizona 方面的問題，您有權利免費以您的母語得到幫助和訊息。洽詢一位翻譯員，請撥電話，在此插入數字 877-475-4799。

Vietnamese: Nếu quý vị, hay người mà quý vị đang giúp đỡ, có câu hỏi về Blue Cross Blue Shield of Arizona quý vị sẽ có quyền được giúp và có thể thông tin bằng ngôn ngữ của mình miễn phí. Để nói chuyện với một thông dịch viên, xin gọi 877-475-4799.

Arabic: إن كان لديك أو لدى شخص تساعده أسئلة بخصوص Blue Cross Blue Shield of Arizona، فإن لديك الحق في الحصول على المساعدة والعلومات الضرورية بلغتك من دون أي تكلفة. للتحدث مع مترجم أتصل ب 877-475-4799.
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Multi-Language Interpreter Services: (cont.)

Tagalog: Kung ikaw, o ang iyong tinutulungan, ay may mga katanungan tungkol sa Blue Cross Blue Shield of Arizona, may karapatan ka na makakuha ng tulong at impormasyon sa iyong wiwa ng walang gastos. Upang makausap ang isang tagasalin, tumawag sa 877-475-4799.

Korean: 만약 귀하 또는 귀하가 돕고 있는 어떤 사람이 Blue Cross Blue Shield of Arizona에 관해서 질문이 있다면 귀하의 도움과 정보를 귀하의 언어로 비용 부담없이 얻을 수 있는 권리가 있습니다. 그렇게 동역사와 매겨하기 위해서는 877-475-4799로 전화하십시오.

French: Si vous, ou quelqu’un que vous êtes en train d’aider, a des questions à propos de Blue Cross Blue Shield of Arizona, vous avez le droit d’obtenir de l’aide et l’information dans votre langue à aucun coût. Pour parler à un interprète, appelez 877-475-4799.

German: Falls Sie oder jemand, dem Sie helfen, Fragen zum Blue Cross Blue Shield of Arizona haben, haben Sie das Recht, kostenlose Hilfe und Informationen in Ihrer Sprache zu erhalten. Um mit einem Dolmetscher zu sprechen, rufen Sie bitte die Nummer 877-475-4799 an.

Russian: Если у вас или лица, которому вы помогаете, имеются вопросы по поводу Blue Cross Blue Shield of Arizona, то вы имеет право на бесплатное получение помощи и информации на вашем языке. Для разговора с переводчиком позвоните по телефону 877-475-4799.

Japanese: ご本人様、またはお客様の身の回りの方でも、Blue Cross Blue Shield of Arizonaについてご質問がございましたら、ご希望の言語でサポートを受けたり、情報を入手したりすることができます。料金はかかりません。通訳とお話される場合、877-475-4799 までお電話ください。

Farsi: 
آگه شما، یا کسی که شما به او کمک میکنید، سوالات مورد اطلاعاتی به زبان خود را به مشاور رایگان دریافت کنید 877-475-4799. اکثر حاضر می‌باشد.

Assyrian:

Serbo-Croatian: Ukoliko Vi ili neko kome Vi pomažete ima pitanje o Blue Cross Blue Shield of Arizona, imate pravo da besplatno dobijete pomoć i informacije na Vašem jeziku. Da biste razgovarali sa prevodiocem, nazovite 877-475-4799.

Thai: หากคุณ หรือคุณช่วยเหลือคนอื่นเกี่ยวกับ Blue Cross Blue Shield of Arizona คุณมีสิทธิ์ได้รับความช่วยเหลือและข้อมูลในภาษาของคุณโดยไม่มีค่าใช้จ่าย ติดต่อตาม โทร 877-475-4799.