FORCE
Facing Our Risk of Cancer Empowered
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May 29, 2019

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RE: Reconsideration of National Coverage Determination (NCD) 90.2 for Next Generation Sequencing (NGS) for Medicare Beneficiaries with Advanced Cancer (CAG-00450R)

Dear Director Jensen:

We are pleased to submit the following comments regarding Section 90.2 of the Medicare National Coverage Determinations (NCD).

Section 90.2 of the Medicare National Coverage Determinations (NCD) Manual states conditions of coverage for NGS. This section is being interpreted to apply to NGS tests for somatic and germline mutations, and states that a patient must meet the following criteria to qualify for NGS testing:

- either recurrent, relapsed, refractory, metastatic, or advanced stage III or IV cancer; and,
- either not been previously tested using the same NGS test for the same primary diagnosis of cancer, or repeat testing using the same NGS test only when a new primary cancer diagnosis is made by the treating physician; and,
- decided to seek further cancer treatment (e.g., therapeutic chemotherapy).

Additionally, the policy stipulates that the diagnostic laboratory test using NGS must have:

- Food & Drug Administration (FDA) approval or clearance as a companion in vitro diagnostic; and,
- an FDA-approved or -cleared indication for use in that patient's cancer; and,
- results provided to the treating physician for management of the patient using a report template to specify treatment options.

Specifically we have the following concerns with this policy:

- **FDA-approved or -cleared companion in vitro diagnostic and indication prerequisite.** This requirement will limit access to most genetic tests for the presence of a germline mutation. The majority of diagnostic lab tests are not FDA-approved; but are CLIA-certified. CMS regulates all laboratory testing (except within research) so prohibiting coverage of tests that lack the FDA-approval is contradictory and will harm patients with germline mutations.

- **Requirement for the laboratory test to have an FDA-approved or -cleared indication for use in that patient's cancer.** Similarly, limiting coverage to only those tests with an approved targeted therapy eliminates utilization of tests that may inform other medical decisions including the aggressiveness of surgery and/or therapy. The NCA Tracking Sheet indicates that the agency is "only reconsidering the evidence available for tests of germline mutations to identify those with hereditary cancer who may benefit from targeted treatments based on results of the test; all other tests are beyond the scope of this reconsideration." These criteria are overly restrictive as germline testing has significant value beyond identifying those who may benefit from current FDA-approved targeted treatments. For example, germline testing can inform surgical decisions about lumpectomy and radiation vs. mastectomy and surgical vs. medical estrogen suppression. Results of germline testing can guide adjuvant chemotherapy decisions for breast cancer as well.

- **Restricting testing only to those with current, relapsed, refractory, metastatic, or advanced stage III or IV cancer.** Prior to implementation of this policy, Local Coverage Determinations (LCDs) provided for germline genetic testing of Medicare beneficiaries diagnosed with cancer who met established, evidence-based criteria. The LCDs were designed to provide reasonable and necessary medical care. The NCD overrides these policies and significantly limits testing for germline mutations. This will effectively end coverage for individuals with earlier stage cancers whose treatment decisions depend on germline testing. Germline testing should not be reserved for only those people who have advanced or metastatic disease. The promise of personalized and precision medicine is the ability to detect cancer early—or to prevent it altogether. This NCD fails to provide the standard of care to cancer patients by limiting germline testing to those with recurrent, relapsed, refractory, metastatic, or advanced stage III or IV disease. An estimated 60% of cancers in the Medicare population are diagnosed at stage I or II; approximately 10% of cancers—20% of ovarian cancers—are likely hereditary.

  While prevention is not Medicare's mandate, stopping early stage disease from advancing is a valuable and viable endpoint. When a hereditary cancer syndrome is suspected, testing the oldest affected relative for a mutation first is clinically appropriate. If the affected family member happens to be a Medicare beneficiary, s/he should not be precluded from testing as a result of the coverage criteria outlined in this NCD. While Medicare is prohibited from covering preventive services unless explicitly authorized by Congress, a person who has "signs, symptoms, complaints, or personal histories of disease" meets the criterion for

coverage under Medicare guidelines. Further, these individuals do not qualify for coverage for BRCA testing as outlined by the USPSTF Guidelines which exclude patients with symptoms or in active treatment.

A 2018 study published in the Annals of Surgical Oncology found that "a substantial number of Medicare patients with clinically actionable genetic variants are being missed by current testing criteria" and suggested the need for significant expansion and simplification of the testing criteria for HBOC.[1] Many cancers related to germline mutations are treatable with therapies that are not specific to the mutation or disease—but the genetic variant impacts treatment response and outcomes. For instance, BRCA-mutated tumors are particularly sensitive to platinum drugs but their use is generally limited to first-line treatment due to development of resistance.[2] A number of studies have shown that rates of genetic testing for hereditary cancer are well below what they should be given current clinical guidelines—especially among minority populations.[3,4,5,6,7,8,9,10]

The rationale for restricting germline testing to those with advanced stage disease and an FDA-approved or -cleared companion in vitro diagnostic and therapeutic indication, as defined in the NCD, may be due to the limited number of existing drug approvals, which currently focus on later-stage disease. These are not reflective of the comprehensive value of germline testing which can guide clinical management, surgical and radiation decisions, therapy choices, and more. NGS-based germline testing has demonstrated utility in earlier cancer settings. Testing individuals who meet evidence-based criteria before they recur or have advanced stage disease serves the patient population by identifying the best treatment options regardless of disease stage.

Extensive research on use of PARP inhibitors and other agents in stage II disease in mutation carriers is underway. The current limitations based on cancer stage will not allow this policy to adapt as new indications are approved. Further, genetic testing is needed to determine eligibility for participation in treatment clinical trials for people with early stage disease, including clinical trials for adjuvant therapy in breast cancer.

- **Focus on a technology vs. a test.** This NCD focuses on a technology (NGS) rather than a test and its purpose. This approach may work for some medical or diagnostic technologies, but not NGS given its varied uses. NGS is a sequencing methodology utilized to capture genomic data—not a specific test. Unlike Sanger sequencing which typically provides sequence information for a single DNA strand or molecule, NGS enables sequencing of a large number of DNA molecules simultaneously. As evidenced by the original application for this NCD, NGS tests for use in cancer are often comprised of gene panels whose content is relevant to specific or multiple tumor types.

  Application of this policy to germline testing is problematic. Individuals who undergo germline genetic testing via Sanger sequencing are eligible for Medicare coverage of the test under LCDs regardless of cancer stage as long as they meet the stated personal and family

history or ethnic criteria. These policies align with national, evidence-based expert guidelines. Conversely, people who have a germline test for the exact same purpose via NGS technology fail to qualify for coverage unless they meet the NCD criteria, which is significantly more restrictive. This inconsistency is illogical.

A clinician ordering a medically necessary germline genetic test cannot be expected to know whether the lab is using NGS or another technology to process the sample. This presents a barrier to care. Equal access to, and coverage of, germline testing regardless of the technology utilized is imperative. NGS is generally more efficient and cost-effective than older sequencing methods—and the majority of U.S. labs now use this technology, even for "basic" BRCA1/2 testing.

National Guidelines

Evidence-based guidelines and recommendations from a broad range of professional societies support the use of germline genetic testing in certain patients, regardless of cancer stage or an FDA-approved or -cleared diagnostic and therapy for the disease. The National Comprehensive Cancer Network provides guidelines that outline who should be offered genetic testing for hereditary cancer risk and how individuals should be managed based on test results. The American Society of Clinical Oncology states that recognition and management of individuals with an inherited susceptibility to cancer are core elements of oncology care. It recommends genetic testing when there is personal or family history suggestive of genetic cancer susceptibility, the test can be adequately interpreted, and the results will aid in diagnosis or medical management of the patient or family member who has hereditary risk for cancer.[11] The Society of Gynecologic Oncologists recommends genetic testing for all women diagnosed with epithelial ovarian, tubal, and peritoneal cancers, even in the absence of a family history.[12] Additionally, SGO guidelines indicate that all women diagnosed with endometrial cancer should undergo systematic clinical screening for Lynch syndrome (review of personal and family history) and/or molecular screening, when resources are available.[13] The American Society of Breast Surgeons recommends that genetic testing be made available to all patients with a personal history of breast cancer. They also suggest that patients who had genetic testing previously—and no pathogenic variant was identified—may benefit from updated testing.[14] The American College of Medical Genetics and National Society of Genetic Counselors have guidelines on referral and testing for 28 of the most common hereditary cancer susceptibility syndromes.[15]

Clinical utility of germline testing

Cancer is recognized as a disease of older adults, with over 50% of new cases being diagnosed after age 65. While hereditary cancers often occur at younger ages, older onset cancers also can have a familial component.[16,17] The most common germline mutations are associated with Lynch syndrome and BRCA1/2, affecting approximately 1 in 300 and 1 in 400 Americans respectively. Knowledge of a mutation frequently influences surgical decisions, treatment options, and prognosis. This information provides physicians with more accurate assessments of cancer risk for other organs, allowing them to tailor health care strategies that may reduce the disease-burden and mortality associated with these syndromes.

Germline mutations are associated with increased risk of a variety of cancers and confer significant risk of increased morbidity and additional primary cancers. Following is an overview of a few hereditary cancers for which knowledge of a pathogenic mutation conveys clinically actionable interventions.

- **Breast cancer -** There are significant differences in response to treatment based on mutation status. For instance, BRCA1 mutation carriers with hormone-negative breast cancers show less sensitivity to taxane chemotherapy.[18] Germline BRCA mutations are positive selection criteria for use of platinum-based regimen and potentially PARP inhibitors.[19] An estimated 20% of triple-negative breast cancer (TNBC) patients are BRCA mutation carriers and 70% of breast cancers that develop in BRCA1 mutation carriers are triple-negative. A germline BRCA mutation is the sole biomarker to identify TNBC patients that will respond to carboplatin therapy. As such, the BRCA-mutated TNBC subgroup should receive platinum derivatives as part of their neoadjuvant (and/or adjuvant) treatment.

  A germline mutation also impacts surgical decision-making in breast cancer. Without it, women may receive suboptimal care. While someone without a germline mutation may opt for lumpectomy and radiation, a women with a high-risk mutation would be advised to undergo a double mastectomy. Rates of contralateral breast cancer after either breast-conserving therapy or unilateral mastectomy are increased in women with BRCA1/2 mutations when compared to patients with sporadic breast cancer. Bilateral mastectomy confers no survival advantage to most women, but those who carry pathogenic mutations in genes such as BRCA1/2 are the rare exceptions.[20] Additionally, women with breast cancer, who test positive for a BRCA mutation, are at significantly increased risk of developing ovarian cancer. Knowledge of this risk enables the patient and her health care team to be more vigilant regarding additional primary cancers.

- **Colorectal cancer -** There is considerable stage-independent variability in colorectal cancer outcomes. This inconsistency underscores the need for prognostic and predictive biomarkers to guide therapeutic decision-making. Consequently, many colorectal cancer patients benefit from microsatellite instability testing before the cancer is advanced or metastatic followed by germline testing as appropriate. Current guidelines suggest genetic evaluation for all newly diagnosed patients with colorectal cancer (alternatively, those diagnosed prior to age 70 years), or based on other criteria such as family history or diagnosis of endometrial cancer before age 60.[21]

  For those with Lynch syndrome, more extensive colectomy is typically recommended.[22, 23] Risk of uterine and ovarian cancer as well as gastric, urinary tract, and small bowel cancer is increased in Lynch syndrome patients. Knowledge of these risks leads to greater patient and provider awareness, which may result in earlier diagnosis of additional primary cancers.

- **Ovarian cancer -** More than one in five ovarian carcinomas are associated with germline mutations. The Society for Gynecologic Oncologic indicates that 15% are attributable to a BRCA mutation. An additional 5-6% have other germline mutations including the Lynch syndrome genes (MLH1, MSH2, MSH6, PMS2), and BRIP1, RAD51D, RAD51C, PALB2, BARD1, and TP53.[24]

  A study published in 2011 looked at women newly diagnosed with ovarian, fallopian tube, or primary peritoneal cancer. Of those tested, 18% carried a mutation in the BRCA genes, and 6% carried mutations in other genes, such as TP53, RAD51C, RAD50, PALB2, MSH6, CHEK2, BRIP1, and BARD1. Over 35% of the women were diagnosed after age 65. Age at ovarian cancer diagnosis was not generally associated with the likelihood of harboring an inherited mutation or with the gene in which a mutation was found.[25]

  In a 2016 study of nearly 2000 patients with ovarian cancer, 18% carried pathogenic germline mutations in 11 genes associated with increased risk, with the majority (15%) having mutations in BRCA1 or BRCA2. Median age range for the mutations ranged from ages 47 to 65.5 with many of the cancers affecting the over 65 population.[26]

  Studies confirm that BRCA-related cancers often behave and respond to treatment differently than sporadic cancers.[27] They have a better response to platinum therapy compared to patients without BRCA mutations.[28] Likewise, BRCA mutation carriers appear to be more sensitive to the benefits of intraperitoneal chemotherapy.[29,30]

- **Prostate cancer -** Germline testing may have significant diagnostic and therapeutic utility, as demonstrated by the identification of pathogenic germline alterations in men with castration-resistant prostate cancer who respond to PARP inhibition.[31] Aggressive therapy in early-stage BRCA-positive prostate cancers, particularly those with germline BRCA2 mutations, is indicated. The combination of early radical local treatment (e.g. radical prostatectomy or radiotherapy) with adjuvant systemic therapy is indicated in these patients. A 2018 study confirmed that much like BRCA2-related breast and ovarian cancers, men with BRCA2-associated castration-resistant prostate cancers respond better to carboplatin-based chemotherapy than non-BRCA+ prostate cancers.

  There is growing evidence of the presence of germline mutations in men with prostate cancer, and the clinical utility of these findings. A recent study reported in *JAMA Oncology* by Nicolosi et al, found that 17% of men with prostate cancer had germline genetic mutations. BRCA variants accounted for over 30% of the mutations and a number of variants with known therapeutic implications (CHEK2, ATM, PALB2, MUTYH, etc.) were identified.[32] Refusing to test men with earlier stage disease who meet family history criteria is a missed opportunity to provide the appropriate treatment regimen and to inform increased risk of other cancers.

- **Pancreatic cancer -** NCCN and ASCO guidelines recommend germline testing for all individuals with pancreatic cancer. A 2018 study of 3030 patients with pancreatic cancer showed that 6 germline mutations accounted for 5.5% of the patients (ATM, BRCA2, CHEK2, BRCA1, PALB2, and CDKN2A). The mean age at diagnosis was 65.3, with over 60% of the mutation carriers diagnosed after age 60.[33] Knowledge of an inherited mutation is increasingly important for pancreatic cancer patients when making treatment decisions because BRCA-associated cancers may respond better to certain treatments, such a PARP inhibitors and/or a regimen that includes oxaliplatin, a platinum-containing drug used in some pancreatic cancer.[34]

Contraindications
As written, the policy will harm patients and cost Medicare more money due to ineffective or inappropriate treatments. In addition to guiding optimal surgical and therapeutic decisions, germline testing identifies patients for whom there may be contraindications. For instance, Lynch syndrome patients with stage II MSI-H tumors do not benefit from 5-FU adjuvant therapy. In the case of breast cancer, patients suitable for Accelerated Partial Breast Irradiation (APBI) are women over age 60 who are not carriers of a BRCA1/2 mutation.

Closing Comments
This NCD should strive to provide reasonable and necessary care that aligns with current—and emerging—evidence-based guidelines and medicine. Germline tests in appropriate patients have demonstrated utility, "meaning that they inform clinical decision-making and facilitate the prevention or amelioration of adverse health outcomes."[35]

We recognize that the Medicare population may have unique considerations in regard to care. Genetic testing as well as cancer screening, surgical, and treatment decisions require individualizing the benefits and risks of these interventions. Screening and treatment decisions for older adults should consider their general health, life expectancy, cognition, risk of disease and preferences.[36, 37] Screening may benefit older people by finding cancers at an earlier stage when they may be easier to treat.[38, 39] Life expectancy estimates combined with personalized cancer risk profiles can be used to help determine the benefits and risks of different cancer-related tests and interventions.

In summary, germline mutations convey higher risk for 2nd or 3rd primary diagnoses. They affect men and women, young and old, and affect certain ethnic groups disproportionately. Germline testing impacts clinical management, surgical and radiation decisions, system and therapy treatment choices (including access to clinical trials and avoiding unnecessary toxic chemotherapy), screening frequency, intensity, interventions, and most importantly, improves cancer outcomes and survival.

Restriction of patient access to potentially lifesaving tests raises significant concerns. Knowledge of a germline mutation can benefit the individual, their family, and society in general. We urge CMS to seriously consider the implications of this NCD and to take the steps necessary to ensure

that it does not have negative repercussions for the patient community in regard to access to care and the potential benefits of precision medicine.

While not our area of expertise, we would like to mention that the hematologic cancer community has essentially been left out of this process due to the "advanced stage III or IV" disease stipulation. Lymphoma and leukemia, for instance, do not manifest solid tumors and are staged differently than tumor-based cancers. As such, we urge CMS to reconsider the wording of the "criteria to qualify for NGS testing" in order to accommodate access to NGS testing for all cancer patients who may benefit.

Based on the information provided herein, we recommend that NCD 90.2 be revised to indicate that NGS-based germline genetic tests are exempt from the policy. This National Coverage Determination should specifically apply to somatic mutation testing and be renamed:

National Coverage Determination (NCD90.2): Next Generation Sequencing (NGS) for Somatic Mutations

On behalf of our organizations and the patient communities we represent, thank you for your time and consideration. We welcome the opportunity to discuss our comments and concerns with CMS staff.

Sincerely,

AliveAndKickn
Alstrom Syndrome International
American Society of Breast Surgeons
Association of Community Cancer Centers (ACCC)
Breast Cancer Comfort Site
CCARE Lynch Syndrome
Cholangiocarcinoma Foundation
FORCE: Facing Our Risk of Cancer Empowered
Foundation for Women's Cancer
Genetic Alliance
HIS Breast Cancer Awareness
Inflammatory Breast Cancer Research Foundation
M-CM Network
My Gene Counsel, LLC
National Association of Nurse Practitioners in Women's Health (NPWH)
National Patient Advocate Foundation
Ovarian Cancer Research Alliance
Prevent Cancer Foundation
PXE International
SHARE
Sharsheret

Society of Gynecologic Oncology
Stupid Cancer
Spastic Parapalegia
Tigerlily Foundation
Triage Cancer
Young Survival Coalition

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