Next Generation Sequencing (NGS) for Medicare Beneficiaries with Advanced Cancer (CAG-00450R)

Organization:
American College of Medical Genetics and Genomics (ACMG)

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Comment:
The American College of Medical Genetics and Genomics (ACMG) welcomes the opportunity to comment on Next Generation Sequencing (NGS) for Medicare Beneficiaries with Advanced Cancer. ACMG is the only nationally recognized professional membership organization dedicated to improving health through the practice of medical genetics and genomics. Our membership includes over 2000 genetics professionals, nearly 80% of whom are board-certified clinical and laboratory geneticists and genetic counselors.

ACMG appreciates CMS's decision to nationally cover next generation sequencing (NGS)-based testing for patients with advanced cancers. However, we are very concerned that the new policy, communicated through NCD 90.2, was written such that it not only excluded NGS-based testing for patients with earlier stage cancers, but it even prevents Medicare Administrative Contractors (MACs) from making such coverage decisions locally. In fact, many MACs already had local coverage determinations (LCDs) in place that covered testing for germline variants associated with *BRCA1, BRCA2*, and Lynch syndrome in cancer patients that met certain criteria. Implementation of NCD 90.2 effectively eliminated those local coverage policies. Even more concerning, it does not appear that CMS evaluated any evidence to support removing these germline coverage policies for patients with early stage cancer. Section II.C. of CMS's decision memo (CAG #00450N) specifically states that "*the scope of this review is limited to patients with advanced cancer*".

Genetic testing is crucial for patients with hereditary cancers as identification of germline variants may inform treatment decisions and overall management of the patient. Further, this new policy only prevents coverage of NGS-based testing for early stage cancer patients and appears to leave MACs the option to cover older and less cost-effective sequencing methods (e.g., PCR or Sanger sequencing) for these same patients. **ACMG requests that CMS revise this harmful and illogical policy decision and ensure that all Medicare beneficiaries diagnosed with cancer have access to the testing necessary to provide them with the most appropriate treatment.**

As our understanding of the contribution of genetic variants to disease has expanded, somatic and germline testing in patients diagnosed with cancer has become a common practice. Some variants provide prognostic information that informs the potential aggressiveness of a disease while others may be more predictive in nature and aid in predicting benefits or resistance to certain treatments. Together, genetic variants, including germline variants, guide targeted treatments which include surgical decisions,

aggressiveness of treatment, selection of targeted therapeutics, or avoidance of certain therapeutics in both patients with early stage and advanced cancer.

Patient management and surgical decision based on germline variants

Somatic testing of the tumor itself can provide valuable information about the potential aggressiveness of the cancer, but germline testing for hereditary cancer also provides important information including identification of variants associated with high recurrence of cancer. While family history may suggest presence or absence of hereditary cancer, confirmation requires germline testing which is widely available in the United States. Identification of certain hereditary cancers, such as Lynch syndrome, greatly impacts treatment decisions. For example, identification of a hereditary cancer associated with a high risk of cancer recurrence and may lead to more aggressive surgical recommendations by the treating physician, especially for patients with non-advanced cancer. This is particularly true for Lynch syndrome which increases a person's risk for colorectal cancer, endometrial cancer, and many others.

For example, numerous reports indicate that patients with Lynch syndrome who undergo segmental colectomy following diagnosis with colon cancer have an increased risk of subsequent adenoma or colorectal cancer compared with individuals who undergo extended colectomy.[1,2,3,4,5] Therefore, germline test results identifying pathogenic variants in mismatch repair genes associated with Lynch syndrome are used to guide surgical treatment decisions for patients diagnosed with colon cancer, including stage I-III cancer. Similar observations have been made for patients with Lynch syndrome diagnosed with rectal cancer. Those who undergo proctectomy after their first diagnosis have an increased risk of developing metachronous colon cancer compared to those who undergo a total proctocolectomy.[6,7] For both examples, opting for more extensive surgeries in these high-risk cancer patients based on germline genetic information reduces the risk of subsequent colorectal cancer, thus reducing the likelihood for additional surgical procedures and associated costs.

Women with Lynch syndrome also have an increased risk for developing ovarian cancer, and total hysterectomy and/or bilateral salpingo-oophorectomy (BSO) may be recommended as a strategy to reduce the risk of developing ovarian cancer.[8,9] Although specific recommendations are not provided at this time, National Comprehensive Cancer Network (NCCN; https://www.nccn.org/) guidelines identify BSO as a potential risk-reducing option that should be considered on an individualized basis.

As another example, numerous genes have been associated with hereditary breast cancer such as *BRCA1, BRCA2, PALB2, ATM, BRIP1, CDH1, RAD51C, CHEK2*, among others. Germline variants in some of these high-risk hereditary breast cancer genes are associated with a high recurrence of breast cancer. Identification of such germline variants enables the patient and their physician to make important treatment decisions such as whether to proceed with a lumpectomy, unilateral mastectomy, or bilateral mastectomy. NCCN recommends *BRCA1/BRCA2* testing for patients diagnosed at any age with breast or ovarian cancer if they also meet other criteria, such as having at least one close relative with a history of cancer (https://www.nccn.org/).

NCCN also recommends germline testing for certain patients with an initial diagnosis of prostate cancer. Germline testing recommendations for prostate cancer include *MLH1, MSH2, MSH6, PMS2, BRCA1, BRCA 2, ATM, PALB2, CHEK2*, and possibly others depending on the clinical context (https://www.nccn.org/).Prostate cancer has been associated with hereditary breast and ovarian cancer (HBOC) and Lynch syndrome which indicate an increased risk for additional cancer occurrences and may inform surgical decisions.[10,11,12,13,14]

Selection of therapies based on germline variants

Germline variants may also predict how likely a patient is to respond to certain therapies[15]. For example, in patients with HER2-negative breast cancer, platinum-based therapies may be a treatment option if pathogenic germline *BRCA1* or *BRCA2* are also present (https://www.nccn.org/). Recent studies have demonstrated that advanced or metastatic breast cancer patients with germline *BRCA1/BRCA2* pathogenic variants may benefit with the use of PARP inhibitors,[16,17] and NCCN guidelines already recommend considering PARP-inhibitor monotherapy as a treatment for these (https://www.nccn.org/). There is reason to believe that patients with earlier stages of breast cancer may also benefit from these inhibitors, and clinical trials (NCT03499353) are currently underway to explore this possibility.[18] Studies have also shown a benefit from using PD-1 inhibitors in Lynch syndrome patients with advanced cancers,[19] and clinical trials are now investigating the benefit in patients with earlier stage cancers (NCT03631641).

Government and industry have invested in research whose results successfully translate genomic sequencing data into patient care. This is evident by the many clinical trials ongoing and completed (see https://clinical trials.gov). Genetic information when linked to therapy results in higher quality life for many cancer conditions. Therapies applied without genetic information have the potential to cause harm and increase costs.

Use of genetic test results to identify eligibility for clinical trials

Blocking coverage of genetic tests for Medicare beneficiaries with early stage cancers creates a barrier to access to clinical trials. In recent years we have seen a flurry of targeted cancer therapeutics for patients with metastatic cancer enter into clinical trials and even receive marketing approval by the U.S. Food and Drug Administration (FDA). Due to the nature of clinical trials and the drug review process, it could be problematic to combine subjects with early stage cancer and advanced or metastatic cancer in the same clinical trial. Thus, it is understandable that drug manufacturers would focus their initial clinical trials on patients with advanced or metastatic cancer. However, those same targeted therapeutics hold promise for patients with early stage cancers and are now entering into clinical trials.

For example, a phase II clinical trial (NCT03499353) is currently underway in which talazoparib, a PARP inhibitor already approved by FDA for use in certain patients with locally advanced or metastatic breast cancer, is being studied for neoadjuvant treatment of patients with pathogenic germline *BRCA1* or *BRCA2* variants and early stage triple-negative breast cancer. Multiple phase II clinical trials

(NCT03810105; NCT03570476) for use of olaparib (PARP inhibitor) and/or durvalumab (PD-L1 inhibitor) to treat nonmetastatic prostate cancer are currently recruiting participants. Both olaparib and durvalumab have already been approved by FDA for more advanced cancers, and eligibility for these new trials requires presence of certain deleterious germline or somatic mutations. Another phase II clinical trial (NCT03631641) currently underway is investigating the use of nivolumab, which blocks PD-1, to prevent colon adenomas in patients with Lynch syndrome and a past partial colectomy due to colon cancer. Eligibility for this trial requires identification of a germline mutation in MLH1 or MSH2.

Eligibility for trials such as these often require that patients be diagnosed based on both tumor characteristics and germline variants. As we are entering into an era of targeting therapeutics for early stage cancers, it is critical that these patients have access to the diagnostic tests necessary to determine their clinical trial eligibility.

Alignment with USPSTF Conclusions

The United States Preventive Services Task Force ("USPSTF") has performed a systematic evidence review for *BRCA1 and BRCA2* and concluded, "…women whose family history is associated with an increased risk for deleterious mutations in *BRCA1* or *BRCA2* genes be referred for **genetic counseling** and evaluation for *BRCA* testing." This received a Grade B recommendation. Under the provision of the Patient Protection and Affordable Care Act, Medicare beneficiaries, at the discretion of the Secretary, are eligible to receive free preventive services and screenings that receive an A or B recommendation from the USPSTF. Accordingly, the new CMS policy beneficiaries receive a recommendation for germline *BRCA1/BRCA2* testing, but do not have coverage for the testing itself.

Conclusion

Access to genetic testing can play a very important role in the management of patients diagnosed with any stage of cancer as well as patient decisions about their treatment options. Medicare beneficiaries with any stage of cancer should have access to the diagnostics tests necessary to ensure they are receiving optimal treatment and have access to appropriate clinical trials. Removal of the LCDs covering certain germline hereditary cancer tests that were previously in place represents a step backwards and is contrary to the goals of precision medicine. CMS should revise its coverage policy so that it covers genetic testing, including germline testing based on professional guidelines, regardless of cancer stage and ensures Medicare beneficiaries have access to appropriate treatment.

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