May 29, 2019

Tamara Syrek Jensen, JD  
Director, Coverage and Analysis Group  
Centers for Medicare & Medicaid Services  
7500 Security Boulevard  
Baltimore, MD 21244

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

Dear Ms. Jensen,

Thank you very much for the opportunity to submit comments on the reconsideration of the National Coverage Determination (NCD) on Next Generation Sequencing (NGS) for Medicare Beneficiaries with Advanced Cancer, pursuant to CAG-00450R. Invitae is the fastest-growing clinical genetics company in the United States. Our mission is to bring comprehensive genetic information into mainstream medicine to improve healthcare for patients. We are dedicated to making genetic information affordable and accessible to those who can benefit from it. Invitae’s tests rely primarily on next generation sequencing-based genetic technology for hereditary cancer, neurology, cardiology, pediatrics, metabolics, and reproductive health.

Scope of the NCD and its Reconsideration

Invitae believes that there is compelling support for the clinical utility of germline BRCA1/2 testing using NGS in early stage breast cancer patients to improve outcomes by altering patient management to include higher intensity surveillance and surgical interventions to reduce the risk of contralateral breast cancer and ovarian cancer. We believe that the evidence to support these indications and improve patient care and outcomes continues to rapidly evolve and hence, the coverage of these indications is best left to the local coverage determination (LCD) process, the discretion of the MACs, and/or be considered under separate NCDs. In contrast, the scope of the recently issued NCD and its reconsideration should only include the use of NGS germline testing when used for the purpose of determining whether to use targeted therapies in cancer patients. Targeted therapies are defined by the National Cancer Institute as drugs or other substances that block the growth and spread of cancer by interfering with specific molecules ("molecular targets") that are involved in the growth, progression, and spread of cancer.

Evidence to Support Utility of Germline Testing for Hereditary Cancer

NGS, when properly used, has been established as concordant with Sanger sequencing, and clinical utility data generated by either may be used to establish the clinical utility of germline testing using either technology. The application of NGS technology to germline testing has accelerated rapidly and the associated evidence in support of its analytic validity is well established. In collaboration with Massachusetts General Hospital, Stanford Hospital, we at Invitae performed a head-to-head comparison

1 NCI website Targeted Cancer Therapies.  
of analytic \ of BRCA1 and BRCA2 analysis in 1105 individuals tested for hereditary breast and ovarian cancer (HBOC). There was 100% analytic concordance (presence or absence of the variant) for BRCA1/2 between Sanger sequencing at Myriad (during the period of their monopoly-based hegemony on such testing) and an analysis at Invitae using a 29-gene next-generation sequencing (NGS) panel. Furthermore, in a peer-reviewed, published collaborative study performed by Invitae, the Harvard Laboratory of Molecular Medicine and the National Institute for Standards and Technology, we examined the false positive rate for NGS in a validation set consisting of ~196,000 known and confirmed variants (~174,000 single nucleotide variants and 22,000 indels), derived from “Genome in a Bottle” as well as internal laboratory controls serving as a “truth set”. This set of variants represents three orders of magnitude more data than has been published in any previous studies of confirmation of NGS results. NGS demonstrated a 0.22% false-positive rate for SNVs and 5.9% false positive rate for indels. However, and most importantly, we demonstrated that a classification algorithm we developed using these data flagged 100% of NGS false positives as requiring confirmation (confidence Interval lower bound, 99.8% for SNVs, 98.5% for indels) while minimizing the number of flagged true positives seen with NGS requiring unnecessary confirmation that drives up cost and turn-around-time. Finally, it should not be assumed that Sanger sequencing is “the gold standard” and is always correct. Beck et al. showed that naively assuming that a confirmation assay for NGS results using Sanger sequencing is always correct can introduce more errors than confirmation corrects. Thus, NGS is superior to Sanger sequencing alone in terms of analytic validity when there is appropriate quality control of variant calling software to identify which variants do need confirmation. And hence, the evidence to support clinical utility of Sanger sequencing in germline testing is also applicable to NGS-based testing and we recommend that the Agency consider such evidence in this and future NCDs.

Germline testing using NGS on early stage cancer patients is clinically useful to determine the appropriateness of additional monitoring, surgery and therapeutics that are not targeted, as defined by the National Cancer Institute, including in cancer patients up to age 85. Medicare serves patients both younger and older than 65 years old, and CMS should consider evidence that supports the clinical utility based on testing of adults, without regard to their age. According to the National Cancer Institute and American Cancer Society, the 5-year survival rate for women with stage 0 or stage 1 breast cancer is nearly 100% while the 5-year survival rate for women with stage 3 breast cancer is ~72% and for stage 4 is ~22%. These survival rate data mean that women with earlier stage cancer are more likely to survive and be at risk for bilateral breast cancer and ovarian cancer. Published epidemiological data, combined


in a meta-analysis\textsuperscript{6} by Parmigiani et al. show a substantial residual risk for contralateral breast and ovarian cancer in women over age 65 who would, therefore, benefit from the prophylactic surgical interventions that are known to have a favorable effect on outcomes\textsuperscript{7}.

Figure 1. Residual Risks after age 65 for contralateral breast cancer and ovarian cancer in women with unilateral breast cancer and either a \textit{BRCA1} or \textit{BRCA2} pathogenic mutation.

As a result, surgeons caring for patients with unilateral breast cancer undergoing mastectomies for early stage cancers are increasingly relying on \textit{BRCA1}/\textit{2} analysis using NGS with a rapid turn-around time to allow pre-surgical diagnosis of \textit{BRCA1}/\textit{2} in order to decide whether to offer and perform bilateral mastectomies to manage the well documented increased risk of 30-60\% for a contralateral cancer developing in women aged 65\textsuperscript{8}. This strategy reduces the need for two operations, with the attendant increased risks and costs associated with surgical procedures. The utility of making a diagnosis of HBOC by \textit{BRCA1}/\textit{2} analysis is equally obvious given the increased risk of ovarian cancer in women of a Medicare-eligible age and the demonstrated beneficial effect on clinical outcomes in patients undergoing bilateral salpingo-oophorectomy\textsuperscript{9}.

Given the outcomes data described above, it is no surprise that the newest version of the Guidelines of the National Comprehensive Cancer Network (January of 2019) recognizes the benefits of determining

\begin{itemize}
  \item \textsuperscript{6} \url{https://ask2me.org}
  \item \textsuperscript{9} Domchek SM, Friebel TM, Singer CF et al. Association of Risk-Reducing Surgery in \textit{BRCA1} or \textit{BRCA2} Mutation Carriers with Cancer Risk and Mortality (2010) JAMA 304(9): 967-975.
\end{itemize}
BRCA1/2 mutation status in women with breast cancer, including women in the Medicare age range, and recommends additional monitoring and surgery in BRCA1/2 carriers. These guidelines include:

a. Recommend annual mammogram with consideration of tomosynthesis and breast MRI screening with contrast of the contralateral breast in women aged 30-75, in whom unilateral mastectomy only was performed.
b. Consider risk reducing contralateral mastectomy at the time of initial surgery.
c. Consider risk reducing salpingo-oophorectomy (RRSO) ideally between ages 35 and 45. However, as shown in the figure above, substantial increased residual risk for ovarian cancer (58% or 30-fold over background in BRCA1 carriers, 30% (15-fold over background for BRCA2) remains that could be reduced by RRSO.

Germline testing using NGS in early stage cancer patients is clinically useful for determining benefits of adjuvant therapy with estrogen receptor modulators or aromatase inhibitors. In addition to the changes in surgical management and surveillance that are recommended as beneficial in BRCA1/2 carriers with early stage or surgically treated unilateral breast cancer, there is also evidence that adjuvant endocrine therapy is beneficial in terms of disease-free survival following surgery using estrogen receptor modulators or aromatase inhibitors in post-menopausal BRCA1/2 positive patients. The selective estrogen receptor modulator tamoxifen was found to be significantly associated with reduced risk of contralateral breast cancer among both BRCA1 and BRCA2 carriers (summary RR 0.56, 95% CI 0.41-0.76). Similar findings were observed in BRCA1 mutation carriers (summary RR 0.47, 95% CI 0.37-0.60) and BRCA2 mutation carriers alone (summary RR 0.39, 95% CI 0.28-0.54), respectively. Risk reduction was seen even with relatively short durations of tamoxifen (eg 2 years). Aromatase inhibitor anastrazole is indicated for adjuvant treatment of postmenopausal women with hormone receptor-positive early breast cancer. Aromatase inhibitor exemestane is indicated for adjuvant treatment of postmenopausal women with estrogen-receptor positive early breast cancer who have received two to three years of tamoxifen and are switched to exemestane for completion of a total of five consecutive years of adjuvant hormonal therapy. NCCN Guidelines reference retrospective data that aromatase inhibitors such as exemestane or anastrozole used as adjuvant therapy can reduce the risk of contralateral breast cancer in BRCA1/2 patients with ER-positive breast cancer. Although patients with BRCA1/2 mutations are not uniquely helped by adjuvant therapy using estrogen receptor modulators or aromatase inhibitors, they obtain substantially greater benefit because their background risk is so much higher than patients who lack such mutations.


Conclusion

In summary, there is compelling support for the clinical utility of germline BRCA1/2 testing using NGS in early stage breast cancer patients to improve outcomes by altering patient management to include higher intensity surveillance and surgical interventions to reduce the risk of contralateral breast cancer and ovarian cancer. Invitae believes that coverage for these indications should be determined by the LCD process, MAC discretion, and/or separate NCDs. In contrast, the recently issued NCD should cover only the use of NGS germline testing for the purpose of determining whether to use targeted therapies as defined by the National Cancer Institute as drugs or other substances that block the growth and spread of cancer by interfering with specific molecules ("molecular targets") involved in the growth, progression and spread of cancer\(^\text{14}\). We respectfully request that the scope of the reconsideration of this NCD be limited to NGS testing to determine eligibility of patients for targeted therapies for patients with late stage cancer, whether testing is for germline or somatic mutations. Coverage for all other testing, including for early stage cancer patients, using NGS should be addressed by the LCD, MAC and/or separate parallel review processes.

On behalf of Invitae, thank you for your ongoing engagement with stakeholders and your willingness to open a reconsideration of the NCD. We believe that the Coverage Analysis Group and CMS strive to ensure Medicare beneficiaries have access to innovative technologies and medical advances to improve their care and outcomes and this reconsideration in another step in that effort. If we may be of further assistance, please contact us at robert.nussbaum@invitae.com or lee.bendekgey@invitae.com.

Sincerely,

Robert L. Nussbaum, M.D.
Chief Medical Officer

Lee Bendekgey
Chief Operation Officer

\(^{14}\) NCI website Targeted Cancer Therapies.