ConnectedHealth

June 11, 2019

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Centers for Medicare & Medicaid Services
Mail Stop # S3-02-01
7500 Security Boulevard
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RE: *Reconsideration of National Coverage Determination for Next Generation Sequencing (NGS) for Medicare Beneficiaries with Advanced Cancer* (CAG-00450R)

The Connected Health Initiative (CHI) appreciates the opportunity to provide input to the Centers for Medicare & Medicaid Services (CMS) on its reconsideration of evidence available for tests of germline mutations using Next Generation Sequencing (NGS) for Medicare beneficiaries.[1] We support CMS' reopening of the National Coverage Determination (NCD) and endorse CMS' collaboration with industry stakeholders as this NCD is implemented throughout the country. CHI strongly supports the use of NGS tests for the detection of germline mutations and hereditary cancers.

CHI represents a broad consensus of stakeholders across the healthcare and technology sectors. Our mission is to support the responsible and secure use of digital health innovations throughout the continuum of care to improve patients' and consumers' experience and health outcomes. We seek to partner with the Department of Health and Human Services (HHS) in realizing the benefits of an information and communications technology-enabled American healthcare system. In particular, CHI is committed to responsibly advancing the role of technology such as NGS in preventing and treating disease.

CHI appreciates the opportunity to provide comments as CMS considers ways to improve the existing NCD based on available evidence. Diagnostic tools—using artificial/augmented intelligence (AI), powered by streams of data and algorithms—can and should serve as a vital means of realizing the benefits of therapeutics. Access to

[1] *See* National Coverage Analysis Tracking Sheet for Next Generation Sequencing for Medicare Beneficiaries with Advanced Cancer (CAG-00450R), https://www.cms.gov/medicare-coverage-database/details/nca-trackingsheet. aspx?NCAId=296 (Accessed March 26, 2019).

these tools will advance the personalization of healthcare, improve outcomes, and encourage greater proactive engagement by patients.

NGS can and should be utilized for the widest range of use cases possible.[2] CHI fully supports its use for initial assessments, disease tracking, and where the testing of a companion is not possible, among others. CHI further supports CMS' reconsideration of evidence available for germline mutation testing to identify patients with inherited cancers. Such testing aids in finding the most appropriate treatments for those suffering from advanced cancers.

CHI believes that a strong evidence base justifies expanded coverage for NGS. We urge CMS to consider the following non-exclusive collection of evidence that supports expanded NGS coverage:

- Testing for germline mutations (targeted panels, whole exome and genome or mitochondrial DNA testing) has been demonstrated to assist in identifying inherited diseases.[3]
- NGS has been demonstrated to efficiently evaluate samples across bigger panels through a single test – e.g., in addressing breast cancer where 100 percent concordance with Sanger results regarding the identification of single nucleotide alterations, insertions, and deletions were attained (with the exception of three large genomic rearrangements contained in the training set); and where the optimized pipeline applied to the validation set identified pathogenic and polymorphic variants, including a novel BRCA2 pathogenic variant at exon 3, 100% of which were confirmed by Sanger in their correct zygosity status.[4] This study "strongly supports that the Ion Torrent PGM technology in BRCA1 and BRCA2 germline variant identification, combined with MLPA analysis, is highly sensitive, easy to use, faster, and cheaper than traditional (Sanger sequencing/MLPA) approaches."[5]
- In the case of 450 patients with early-onset colorectal cancer (CRC) where 72 (16 percent) had gene mutations, NGS was shown to enable early detection and more effective treatments. Given the high frequency and wide spectrum of

[2] *E.g.*, Cao Y, Fanning S, Proos S, Jordan K and Srikumar S (2017) A Review on the Applications of Next Generation Sequencing Technologies as Applied to Food-Related Microbiome Studies. *Front. Microbiol*. 8:1829. doi: 10.3389/fmicb.2017.01829.

[3] Yohe S, Thyagarajan B. Review of Clinical Next-Generation Sequencing. Arch Pathol Lab Med. 2017 Nov;141(11):1544-1557. doi: 10.5858/arpa.2016-0501-RA. Epub 2017 Aug 7. Review. PubMed PMID: 28782984.

[4] Nicolussi A, Belardinilli F, Mahdavian Y, Colicchia V, D'Inzeo S, Petroni M, Zani M, Ferraro S, Valentini V, Ottini L, Giannini G, Capalbo C, Coppa A. Next-generation sequencing of BRCA1 and BRCA2 genes for rapid detection of germline mutations in hereditary breast/ovarian cancer. PeerJ. 2019 Apr 22;7:e6661. doi: 10.7717/peerj.6661. eCollection 2019. PubMed PMID: 31065452; PubMed Central PMCID: PMC6482939.

[5] *Id.*

mutations, genetic counseling and testing with a multigene panel could be considered for all patients with early-onset CRC.[6]

- NGS testing has been demonstrated to be an accurate approach to screening to detect CRC. A recently-published study validated the use of targeted next generation sequencing to detect microsatellite instability and screen for Lynch syndrome in assessing a cohort of 645 upper gastrointestinal tract cancers, targeted next generation sequencing assessed microsatellite instability by identifying characteristic insertion and deletion mutations where targeted sequencing as the initial screening test helped seven of 645 of patients identify pathogenic germline variants confirming a diagnosis of Lynch syndrome.[7]

CHI believes that the evidence demonstrates that NGS technology's use in germline testing is vital, empowering much earlier detection and treatment of disease at more efficient costs. Further, the use of NGS helps to personalize medicine, making Medicare beneficiaries more proactively engaged in their own care.

CMS should, in as flexible an approach as possible, expand coverage to patients with earlier stage cancers and applications for repeat NGS testing in order to permit identification of cancer at the earliest point possible to improve outcomes and to encourage proactive health changes. CHI also notes its concern with CMS' previous determination to prohibit coverage of repeat NGS-based testing for patients with earlier stage cancer, and (based on strong evidence) we urge for CMS to revisit this interpretation to permit the use of repeat NGS testing to assist in tracking of cancer once diagnosed.

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[6] Pearlman R, Frankel WL, Swanson B, Zhao W, Yilmaz A, Miller K, Bacher J, Bigley C, Nelsen L, Goodfellow PJ, Goldberg RM, Paskett E, Shields PG, Freudenheim JL, Stanich PP, Lattimer I, Arnold M, Liyanarachchi S, Kalady M, Heald B, Greenwood C, Paquette I, Prues M, Draper DJ, Lindeman C, Kuebler JP, Reynolds K, Brell JM, Shaper AA, Mahesh S, Buie N, Weeman K, Shine K, Haut M, Edwards J, Bastola S, Wickham K, Khanduja KS, Zacks R, Pritchard CC, Shirts BH, Jacobson A, Allen B, de la Chapelle A, Hampel H; Ohio Colorectal Cancer Prevention Initiative Study Group. Prevalence and Spectrum of Germline Cancer Susceptibility Gene Mutations Among Patients With Early-Onset Colorectal Cancer. JAMA Oncol. 2017 Apr 1;3(4):464-471. doi: 10.1001/jamaoncol.2016.5194. PubMed PMID: 27978560; PubMed Central PMCID: PMC5564179.

[7] Christakis AG, Papke DJ, Nowak JA, Yurgelun MB, Agoston AT, Lindeman NI, MacConaill LE, Sholl LM, Dong F. Targeted Cancer Next Generation Sequencing as a Primary Screening Tool for Microsatellite Instability and Lynch Syndrome in Upper Gastrointestinal Tract Cancers. Cancer Epidemiol Biomarkers Prev. 2019 Apr 26. pii: cebp.1250.2018. doi: 10.1158/1055-9965.EPI-18-1250; PubMed PMID: 31028081.

CHI appreciates the opportunity to submit its comments to CMS on this important matter. We look forward to assisting CMS in realizing an advanced technology-enabled care continuum that provides maximum value to patients at the lowest costs.

Sincerely,

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