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RE: Proposed Decision Memo for Next Generation Sequencing (NGS) for Medicare Beneficiaries with Advanced Cancer (CAG-00450R)

Dear Director Jensen:

Thank you for the opportunity to submit comments on behalf of our organizations and the millions of Americans we represent. We are very pleased to see that CMS has heard the concerns of the patient and health care provider community and is making efforts to broaden and further define coverage for NGS-based germline testing.

A. Coverage of NGS Testing in Breast and Ovarian Cancer

In Section A of the Proposed Decision Memo, CMS states that the evidence is sufficient to expand coverage of NGS as a diagnostic laboratory test when the patient has:

- ovarian or breast cancer;
- clinical indications for germline (inherited) testing,
- risk factors for germline (inherited) breast or ovarian cancer; and
- not been previously tested using NGS.

The proposed policy also stipulates that the diagnostic laboratory test using NGS must have all of the following:

- Food and Drug Administration (FDA) approval or clearance;
- 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.

We have a number of concerns with this proposed NCD language:

- **Requirement for both "Clinical indications for germline (inherited) testing" and "risk factors for germline (inherited) breast or ovarian cancer".**

The stipulation that the patient has a diagnosis of ovarian or breast cancer, "clinical indications" and "risk factors" for germline testing and breast or ovarian cancer is duplicative and somewhat ambiguous. For instance, all women with ovarian cancer meet clinical guidelines for germline testing. What additional risk factors must be present to qualify for germline testing? Is a known mutation in the family considered a risk factor? It may be difficult for a clinician to provide evidence of clinical indications and risk factors as these terms can be synonymous.

Suggested Clarification:

To avoid confusion, we recommend that CMS clarify its definition of clinical indications and risk factors. NCCN provides comprehensive recommendations on the appropriate testing of cancer patients. The agency should refer to NCCN for guidance. CMS might also provide examples of clinical indications and risk factors, and revise the language to read:

CMS proposes that the evidence is sufficient to expand coverage of NGS as a diagnostic laboratory test when the patient has:

- *Ovarian cancer; or*
- *Breast cancer, and clinical indications for germline genetic testing including personal or family medical history consistent with an inherited mutation*

• **FDA approval or clearance of the diagnostic laboratory test.**

To our knowledge, there are no FDA-approved or -cleared NGS tests for germline testing in solid tumor cancers. Of the FDA-cleared or -approved NGS diagnostic tests, none specifically detect germline mutations via NGS technology.

- *F1CDx* cannot distinguish between germline and somatic mutations.¹ If the test finds a BRCA1/2 mutation, it is unable to determine whether that mutation is germline or somatic. Therefore, the patient must undergo a subsequent germline test.
- *myChoice* “identifies germline and somatic variants in the tumor but does not distinguish between the two.”² Like *F1CDx*, additional testing is needed if a germline mutation is suspected.
- *MSK-IMPACT* “is intended to provide information on somatic mutations (point mutations and small insertions and deletions) and microsatellite instability.”³ It is not a germline test.

Current FDA-approved germline tests use non-NGS technology (predominantly Sanger sequencing). For example, *BRCAAnalysis CDx* is FDA-approved for germline testing of BRCA1/2 mutations in conjunction with olaparib treatment for advanced or metastatic breast cancer; it is a Sanger sequencing test.

Without an FDA-cleared or approved NGS-based germline test for breast and ovarian cancer, NGS-based germline testing remains non-covered at the national level.

The CMS analysis “includes peer-reviewed, published clinical studies, and guidelines pertaining to using NGS as a diagnostic test to identify germline mutations in the diagnosis of inherited cancers.” Ultimately, CMS concludes, “[a]s a result of current evidence and our present analysis, we now believe that the use of NGS has additional benefits.” Most, if not all, of the resources cited in the proposed decision memo relied upon germline testing from CLIA-certified or academic laboratories without FDA approval or clearance. Germline testing via CLIA-certified laboratories is appropriate and the standard of care. CMS regulates all laboratory testing (except within research) so prohibiting Medicare coverage of NGS tests that lack FDA-approval is incongruous and will harm patients with germline mutations.

Recommended Revision:

We recommend that CMS eliminate the Food and Drug Administration (FDA) approval or clearance requirement for the diagnostic laboratory test.

Alternatively, allow Medicare Administrative Contractors (MACs) to develop local coverage determinations (LCDs) for germline testing of patients with suspected hereditary cancers, including those with breast and ovarian cancer.

- **FDA approved or cleared indication for use in that patient’s cancer.**

The proposed policy states that the diagnostic laboratory test using NGS must have an FDA-approved or -cleared indication for use in that patient’s cancer. This suggests that only an FDA-approved or -cleared indication with a companion diagnostic is acceptable. This is unfeasible since there is no NGS test specifically for the detection of germline mutations. As such, the proposed policy fails to provide coverage of germline testing for breast and ovarian cancer.

As CMS states, the evidence demonstrates that identification of germline mutations guides decision-making and “treatment modalities including chemotherapy, radiotherapy, or surgery” for patients with all stages of cancer. If the lab must have an FDA-approved or -cleared diagnostic test and indication, in essence, CMS is limiting coverage to only those tests with an approved targeted therapy—and again, restricting germline testing to only those patients with recurrent, relapsed, refractory, metastatic, or advanced stage III or IV cancer.

Patients make surgical, radiation, and treatment decisions based on their germline test results. Under the proposed policy language, a patient with earlier stage breast or ovarian cancer is not eligible for any NGS-based testing.

Recommended Revision:

We recommend that CMS eliminate the “FDA approved or cleared therapy for the treatment of breast or ovarian cancer”.

- **Not been previously tested using NGS.**

In most cases, when tumor profiling identifies a somatic mutation in a cancer susceptibility gene, germline genetic testing is advisable. In addition, even if no potentially inherited mutations are found in somatic testing, this does not preclude the possibility of a hereditary cancer mutation. In “When Should Tumor Genomic Profiling Prompt Consideration of Germline Testing?”, the authors note:

- some tumor testing platforms filter out germline variants to improve the accuracy of somatic variant calls,
- acquired changes in the tumor—such as large deletions or chromosomal loss—can mask a germline mutation, and
- not all genes associated with hereditary cancer syndromes are included in somatic test panels.⁴

NGS tests for use in cancer are often comprised of gene panels that are relevant to certain tumor types. A woman with ovarian cancer who has tumor testing via *myChoice*, for instance, may learn that she does not carry a BRCA mutation. However, germline testing is still indicated. *myChoice* does not test for mutations beyond BRCA1/2. In contrast, an NGS-based germline test may identify a mutation in PALB2, ATM, RAD51D, STK11, or one of the Lynch Syndrome mutations, which increase her risk of other hereditary cancers and may change her potential surveillance and treatment plan.

CMS notes that NGS testing for germline mutations “is an important tool in managing other types of hereditary cancer to reduce mortality and improve other health outcomes for Medicare beneficiaries.” NGS has become the standard of care for germline testing. The majority of U.S. labs use this technology, even for “basic” BRCA1/2 testing. Since tumor tests also utilize NGS technology, limiting access to once per lifetime—or once per primary diagnosis—is a flawed approach. This is contrary to national evidence-based guidelines and will result in a significant barrier to appropriate care.

The Palmetto GBA MoIDX LCD on Genetic Testing for Lynch Syndrome recognizes that both germline and somatic testing may be medically necessary in certain circumstances. Its policy supports reflexing from an NGS-based tumor test to germline testing in certain patients.⁵ We support such an approach given the unique value of somatic and germline test results.

Finally, the patient may have had a prior NGS test outside the field of oncology, such as for a cardiomyopathy.

Recommended Revision:

We strongly urge CMS to remove, “The patient has not been previously tested using NGS” requirement. The NCD should allow cancer patients to receive both a somatic and germline NGS-based test when medically appropriate.

- **Intersection with existing NCD language.**

It appears that CMS has developed the germline testing policy independent of the prior NCD, but will insert new language into the existing NCD (Appendix B). As just described, the “not been previously tested using NGS” requirement is found in the proposed germline coverage, while somatic testing eligibility requires that the patient has not been previously tested using the same NGS test before. In addition, CMS proposes no change to Section C, which prohibits coverage for patients who do not have advanced cancer (by reference to B.1.). The resulting combination of old and new text is very confusing. Does an NGS-based tumor test bar an individual from accessing NGS-based germline testing? Or, is the policy specific to the use of the NGS diagnostic? For example, a beneficiary who previously had NGS testing for a somatic mutation would not be eligible for coverage of additional tumor tests for the same cancer, but would be entitled to coverage of NGS testing for a germline mutation. The existing format and language creates uncertainty about how to manage patients needing both a somatic and a germline NGS test.

The focus on a technology (NGS) rather than a test and its purpose may work for some medical or diagnostic technologies, but it is challenging given the varied uses of NGS. Under the current scenario, LCDs enable individuals who undergo germline genetic testing via Sanger sequencing to access tumor testing through the NGS NCD. Conversely, people who have a germline test via NGS technology may fail to qualify for coverage of tumor testing under the proposed language. Many physicians have no knowledge of the lab methods used for genetic tests. This inconsistency will amount to disparate care. Medicare beneficiaries should have equal access to, and coverage of, germline testing regardless of the technology utilized.

We have asked CMS to clarify that a patient may receive both a somatic and germline NGS-based test when appropriate. However, this is the bare minimum. Cancers and their response to treatment change over time. Patients should have an NGS panel for somatic mutations at the time of diagnosis and again upon progression on additional lines of therapy. Many metastatic patients benefit from repeat tumor testing to adapt treatment appropriately.

Recommended Revision:

As outlined above, we urge CMS to remove, “The patient has not been previously tested using NGS” requirement.

Another option: CMS can expand the scope of the existing NCD to cover multiple NGS tests in a patient’s lifetime, with details left to LCDs. This will facilitate accurate identification of targetable mutations and treatments throughout the progression of one’s cancer.

B. MACs and Local Coverage of NGS Testing

Section B of the Proposed Decision Memo gives the MACs authority to develop LCDs for NGS-based germline testing when the patient has:

- a cancer diagnosis other than breast or ovarian cancer,
- clinical indications for germline (inherited) testing,
- risk factors for germline (inherited) cancer other than inherited breast or ovarian cancer, and
- not been previously tested using NGS.

Given that many germline mutations are associated with risk of more than one cancer, it is reasonable to assume that they convey “risk factors for germline (inherited) cancer other than inherited breast or ovarian cancer.” BRCA mutations, for instance, cause increased risk of prostate and pancreatic cancers in addition to breast and ovarian. Like the proposed NGS germline testing policy for those with ovarian or breast cancer, criteria for germline testing of individuals with other cancers is unclear. If a woman is diagnosed with pancreatic cancer and has a family history of ovarian or early-onset breast cancer, is she eligible for NGS-based germline testing under a MAC?

Since there are no FDA-cleared or -approved NGS-based germline tests for breast and ovarian cancer, NGS-based germline testing for breast and ovarian cancer patients appears to be non-covered nationally; and the proposed policy would not permit MACs to cover NGS-based germline tests for these cancers.

Recommended Revisions:

Remove germline testing from the NCD altogether. Revise the coverage policy to allow MAC discretion in coverage of all NGS-based germline tests to ensure that patients with breast and ovarian cancer continue to have access to hereditary cancer testing. The first bullet should be edited to read, “a cancer diagnosis,”

Like Section A above, remove, “The patient has not been previously tested using NGS” condition. The policy should allow cancer patients to receive both a somatic and germline NGS-based test when appropriate.

Cancers Beyond Breast and Ovarian

The most common germline mutations are associated with Lynch syndrome, affecting approximately 1 in 300 Americans. In light of this, it is unfortunate that CMS did not include colorectal and other cancers associated with Lynch syndrome in its evidence review because studies that assess mortality were lacking. Knowledge of a mutation frequently influences surgical decisions, treatment options, etc. This information also provides physicians with more accurate assessments of cancer risk for other organs, enabling them to tailor health care strategies that may reduce disease-burden and mortality.

While overall survival (OS) is certainly the gold standard in clinical research, numerous factors influence OS including patient demographics, prior therapies, and the total number of lines of therapy. Many strong research studies use progression-free survival (PFS) or time to progression (TTP) as endpoints, especially for rare cancers. PFS is relevant to Medicare beneficiaries with cancer. It is an indication of disease control and stabilization as well as health-related quality of life.^{6,7,8,9,10} For patients with germline mutations, the ability to manage morbidity and additional primary cancers is crucial.

It is challenging to have NGS-based germline testing for some cancers (i.e. ovarian and breast) managed at the national level, and others covered under the MACs. We strongly urge CMS to consider giving the MACs authority to develop policies for this testing in all cancer types. Alternatively, the agency should rethink inclusion of these cancers in the proposed NGS germline testing NCD policy:

- **Colorectal cancer** - 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 60.¹¹ 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.

A deleterious mutation in the MMR (MLH1, MSH2, MSH6, and PMS2) or EPCAM gene is required to diagnose Lynch syndrome. Germline testing should be offered:

- to patients with microsatellite unstable tumors by MSI/IHC testing;
- if tumor testing is not feasible and if the clinical suspicion of Lynch syndrome is strong (e.g., individual meets revised Bethesda criteria);
- if a patient meets the Amsterdam criteria, some experts recommend germline testing without prior tumor testing.¹²

For those with Lynch syndrome, more extensive colectomy is typically recommended.^{13,14} 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.

- **Prostate cancer** - All men with metastatic prostate cancer meet NCCN guidelines for germline genetic testing. In a study of 692 men with metastatic prostate cancer unselected for family history of cancer or age of diagnosis, 11.6% had mutations in one of 16 DNA-repair genes (including 5.3% BRCA2, 1.6% ATM, 1.9% CHEK2, 0.9% BRCA1, 0.4 % RAD51D, 0.4% PALB2).¹⁵ Identification of a germline mutation 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.¹⁶

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 the standard of care for 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 (unselected for stage, age at diagnosis or family history) had germline genetic mutations. BRCA variants accounted for over 30% of the mutations and a number of variants with known therapeutic implications were identified (CHEK2, ATM, PALB2, MUTYH, etc.).¹⁷ Not testing men who meet clinical and family history criteria is a missed opportunity to provide appropriate treatment 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 six germline mutations (in the ATM, BRCA2, CHEK2, BRCA1, PALB2, and CDKN2A genes) were seen significantly more frequently in cases than in controls and accounted for 5.5% of the unselected pancreatic cancer patients. The mean age at diagnosis was 65.3, with over 60% of the mutation carriers diagnosed after age 60.¹⁸

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 as PARP inhibitors and/or a regimen that includes oxaliplatin, a platinum-containing drug used in some pancreatic cancer.¹⁹ Results from the POLO clinical trial of the PARP inhibitor olaparib indicate that metastatic pancreatic patients with germline BRCA mutations have significantly longer PFS when treated with maintenance olaparib.²⁰

- **Hematologic cancers** - As with prior versions of this NCD, hematologic cancers essentially have been excluded from this process due to the “recurrent, relapsed, refractory, metastatic, or advanced stage III or IV cancer” prerequisite for somatic testing. Lymphoma and leukemia, for instance, do not manifest solid tumors and are staged differently than tumor-based cancers. We request that the NCD be clear on this issue to ensure that Medicare beneficiaries with hematologic diseases have equal access to standard of care tests using NGS technology. 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.

C. Nationally Non-Covered Services

Section C of the Proposed Decision Memo states, “...NGS as a diagnostic laboratory test for patients with cancer are non-covered if the cancer patient does not meet the criteria noted in section B.1.” Again, this raises questions about the intersection of the germline policy with the existing NCD language around somatic NGS tests. The proposed germline testing policy does not meet the criteria in B.1. so it appears that the services would not be covered.

The non-covered services section is redundant and unnecessary. Stakeholders have repeatedly expressed concern about this provision as the language may be interpreted to broadly limit NGS testing for diagnostics that do not fall under coverage outlined in the NCD. CMS removed this section in the final NCD released in March 2018, but it reappeared in the version sent to the MACs as a transmittal in November 2018.

Recommended Revision:

Abolish the “Nationally Non-Covered Services” section(s) of the proposed NCD.

Closing Comments

While we appreciate the agency's effort, this policy falls significantly short of providing reasonable and necessary care that aligns with current evidence-based guidelines. Portions of the coverage requirements are vague and overly restrictive. This will lead to confusion and impede access to appropriate diagnostic tests—especially for patients with potentially hereditary breast or ovarian cancer.

The hindrance of patient access to tests that potentially save or prolong life raises concerns. We urge CMS to seriously consider the implications of this NCD and to take the necessary steps to ensure that it does not negatively affect the cancer community by limiting access to care and the potential benefits of precision medicine.

Based on the information provided herein, we recommend that NCD 90.2 undergo significant revisions to eliminate or significantly reduce the coverage restrictions. If germline testing remains a component of this policy, it is important that the NCD title reflect the full scope of its coverage. Given that germline testing has clinical utility beyond advanced cancer, the name should be revised:

National Coverage Determination (NCD90.2): Next Generation Sequencing (NGS) for Treatment and Management of Cancer

If, as we have suggested, CMS decides to exempt NGS-based germline genetic tests from the NCD, the policy can be renamed:

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

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
CancerCare
CCARE Lynch Syndrome
Dana-Farber Cancer Institute
Fight Colorectal Cancer
FORCE: Facing Our Risk of Cancer Empowered
Genetic Alliance
HIS Breast Cancer Awareness
Inflammatory Breast Cancer Research Foundation
International Society of Oncology Nurses in Genetics
Li-Fraumeni Syndrome Association
Living Beyond Breast Cancer
Male Breast Cancer Coalition
Metastatic Breast Cancer Alliance
Metastatic Breast Cancer Network
My Gene Counsel
National Ovarian Cancer Coalition

National Patient Advocate Foundation
National Society of Genetic Counselors
No Stomach for Cancer
Ovarian Cancer Research Alliance
Pancreatic Cancer Action Network
Patient Empowerment Network
Prevent Cancer Foundation
Prostate Cancer Foundation
Sharsheret
Society of Gynecologic Oncology
Stupid Cancer
Tigerlily Foundation
Triage Cancer
Us TOO International Prostate Cancer Education & Support
Young Survival Coalition
ZERO - The End of Prostate Cancer

¹ Foundation Medicine Expands Indication for FoundationOne®CDx as a Companion Diagnostic for LYNPARZA® (Olaparib), July 1 2019 Press Release (<http://investors.foundationmedicine.com/news-releases/news-release-details/foundation-medicine-expands-indication-foundationoneercdx>)

² myChoice CDx Technical Information (<https://bit.ly/myChoiceCDxSpecs>)

³ FDA Evaluation of Automatic Class III Designation for MSK-IMPACT (Integrated Mutation Profiling of Actionable Cancer Targets) (www.accessdata.fda.gov/cdrh_docs/reviews/DEN170058.pdf)

⁴ DeLeonardis, Kim, et al. "When Should Tumor Genomic Profiling Prompt Consideration of Germline Testing?" *Journal of Oncology Practice* 2019, 15:9, 465-473 <https://ascopubs.org/doi/full/10.1200/JOP.19.00201>

⁵ Local Coverage Determination (LCD): MoIDX: Genetic Testing for Lynch Syndrome (L35024)

(www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=35024&ver=50&SearchType=Advanced&CoverageSelection=Local&ArticleType=BC%7cSAD%7cRTC%7cReg&PolicyType=Both&s=48&KeyWord=Lynch+syndrome&KeyWordLookup=Title&KeyWordSearchType=Exact&kq=true&bc=IAAAACAAAAAA&)

⁶ Griebisch I, Palmer, et al. "Is progression-free survival associated with a better health-related quality of life in patients with lung cancer? Evidence from two randomised trials with afatinib." *BMJ Open* 2014;4:e005762. doi: 10.1136/bmjopen-2014-005762 (<https://bmjopen.bmj.com/content/4/10/e005762>)

⁷ Kaklamani, VG. "Clinical Implications of the Progression-Free Survival Endpoint for Treatment of Hormone Receptor-Positive Advanced Breast Cancer." *Oncologist*. 2016 Aug;21(8):922-30. DOI: 10.1634/theoncologist.2015-0366. Epub 2016 Jun 2.

(<http://theoncologist.alphamedpress.org/content/21/8/922.full>)

⁸ PracticeUpdate Editorial Team. "ABC4 2017: Increased Progression-Free Survival Translates to Slower Decline in Quality of Life in Advanced Breast Cancer." *PracticeUpdate*, 5 Nov. 2015.

(www.practiceupdate.com/content/abc4-2017-increased-progression-free-survival-translates-to-slower-decline-in-quality-of-life-in-advanced-breast-cancer/60477)

⁹ Solà-Morales, Oriol, et al. "Perspectives to mitigate payer uncertainty in health technology assessment of novel oncology drugs." *Journal of Market Access & Health Policy*, 2019. 7:1, DOI: 10.1080/20016689.2018.1562861 (www.tandfonline.com/doi/full/10.1080/20016689.2018.1562861)

¹⁰ Litton, Jennifer K., et al. "Talazoparib in Patients with Advanced Breast Cancer and a Germline BRCA Mutation." *New England Journal of Medicine*, vol. 379, no. 8, 23 Aug. 2018, pp. 753–763., doi:10.1056/nejmoa1802905. (www.nejm.org/doi/full/10.1056/NEJMoa1802905)

¹¹ Win, Aung Ko, et. al. "Lynch Syndrome (Hereditary Nonpolyposis Colorectal Cancer): Clinical Manifestations and Diagnosis." *UptoDate*. 11 Feb. 2019. (<https://www.uptodate.com/contents/lynch-syndrome-hereditary-nonpolyposis-colorectal-cancer-clinical-manifestations-and-diagnosis>)

¹² Win, Aung Ko, et al. "Lynch Syndrome (Hereditary Nonpolyposis Colorectal Cancer): Clinical Manifestations and Diagnosis." *UptoDate*. 11 Feb. 2019. (www.uptodate.com/contents/lynch-syndrome-hereditary-nonpolyposis-colorectal-cancer-clinical-manifestations-and-diagnosis#H72545600)

¹³ "Lynch Syndrome Factsheet." *The Jackson Laboratory*, Sept. 2019 (www.jax.org/education-and-learning/clinical-and-continuing-education/cancer-resources/lynch-syndrome)

¹⁴ Kawakami, Hisato et al. "Microsatellite instability testing and its role in the management of colorectal cancer." *Current treatment options in oncology* vol. 16,7 (2015): 30. doi:10.1007/s11864-015-0348-2 (www.ncbi.nlm.nih.gov/pmc/articles/PMC4594190/)

¹⁵ Pritchard et al. "Inherited DNA-Repair Gene Mutations in Men with Metastatic Prostate Cancer." *NEJM* 2016 August 4; 375(5): 443–453. doi:10.1056/NEJMoa1603144.

¹⁶ Robinson D, et al. "Integrative clinical genomics of advanced prostate cancer." *Cell*. 2015; 161:1215–28. (www.ncbi.nlm.nih.gov/pubmed/26000489)

¹⁷ Nicolosi, Piper, et al. "Prevalence of Germline Variants in Prostate Cancer and Implications for Current Genetic Testing Guidelines." *JAMA Oncology*, vol. 5, no. 4, 2019, p. 523., doi:10.1001/jamaoncol.2018.6760. (<https://jamanetwork.com/journals/jamaoncology/fullarticle/2723582?resultClick=1>)

¹⁸ Hu, Chunling, et al. "Association Between Inherited Germline Mutations in Cancer Predisposition Genes and Risk of Pancreatic Cancer." *Jama*, vol. 319, no. 23, 2018, p. 2401., doi:10.1001/jama.2018.6228. (<https://jamanetwork.com/journals/jama/fullarticle/2685154>)

¹⁹ Kowalewski, Adam, et al. "Emerging Strategies in BRCA-Positive Pancreatic Cancer." *Journal of Cancer Research and Clinical Oncology*, vol. 144, no. 8, 2018, pp. 1503–1507., doi:10.1007/s00432-018-2666-9. (www.ncbi.nlm.nih.gov/pmc/articles/PMC6061050/)

²⁰ Golan et al. Maintenance olaparib for germline BRCA-mutated metastatic pancreatic cancer. *NEJM* 2019. Jul 25;381(4):317-327. doi: 10.1056/NEJMoa1903387.