

SPECIAL ARTICLE

Genetic counseling, testing and management of prostate adenocarcinoma patients: recommendations from a consensus of experts from the National Institute of Neoplastic Diseases of Peru

Asesoramiento genético, testeo y manejo de pacientes con adenocarcinoma de próstata: recomendaciones de un consenso de expertos del Instituto Nacional de Enfermedades Neoplásicas del Perú

Silvia P. Neciosup^{1,a} , Henry L. Gómez^{1,a} , Analí P. Mora^{1,b} , Rossana Ruiz^{1,c} , Carlos A. Castañeda^{1,c} , Zaida D. Morante^{1,c} , Natalia I. Valdivieso^{1,b} , José R. Pieschacón^{2,d} 

¹ National Institute of Neoplastic Diseases. Lima, Perú.

² Evidentias SAS. Bogotá, Colombia.

^a PhD, ^b MSc, ^c MD, ^d MSE

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Correspondence:

Silvia P. Neciosup
E-mail: silvianeciosup@yahoo.com

ABSTRACT

The objective was to provide tools for genetic profiling and treatment of patients with prostate adenocarcinoma. The Consensus was made up of oncologists and geneticists from the National Institute of Neoplastic Diseases of Peru and followed the guidelines of the "Consensus Conference on Standard Operating Procedures of the European Society of Medical Oncology". The GRADE methodology was applied to assess the evidence and make recommendations. The clinical practice guidelines were graded following the "AGREE II". All patients with prostate adenocarcinoma and risk factors should be ordered genetic testing and counseling. Testing should include *BRCA1/2*, *ATM*, *CHECK2*, *PALB2*, *MLH1*, *MSH2/6*, and *PMS2*. Additional genes may be requested based on the clinical condition. In patients with metastatic castration-resistant or regional prostate cancer, somatic testing may be considered. The result of the test can guide treatment. In conclusion, there are many unmet needs in the approach and management of prostate cancer. Cancer genetic risk assessment and genetic counseling involve the identification and counseling of individuals at risk for hereditary cancer. Genetic counseling and testing are expected to be included in daily clinical practice.

Keywords

Prostate, adenocarcinoma; Genetic Counseling; Genetic Profile; Germline; Consensus; Poly(ADP-Ribose) Polymerase Inhibitors (source: MeSH NLM).

RESUMEN

El objetivo fue proporcionar herramientas para el perfilamiento genético y manejo de pacientes con adenocarcinoma de próstata. El Consenso lo conformaron oncólogos y genetistas del Instituto Nacional de Enfermedades Neoplásicas y siguió los lineamientos de la Conferencia de consenso de procedimientos operativos estandarizados de la Sociedad Europea de Oncología Médica. La metodología GRADE se utilizó para evaluar la evidencia y hacer recomendaciones. Las guías de práctica clínica fueron calificadas siguiendo el "AGREE II". A todo paciente con adenocarcinoma de próstata y factores de riesgo se le debería ordenar testeo y asesoramiento genético; el testeo debería incluir *BRCA1/2*, *ATM*, *CHECK2*, *PALB2*, *MLH1*, *MSH2/6*, y *PMS2*. Genes adicionales pueden solicitarse dependiendo del contexto clínico. En pacientes con cáncer de próstata metastásico resistente a la castración o regional, puede ser considerado el testeo somático. El resultado del testeo puede guiar el tratamiento. En conclusión, existen muchas necesidades insatisfechas en el enfoque y manejo del cáncer de próstata. La evaluación del riesgo genético del cáncer y el asesoramiento genético involucra la identificación y el asesoramiento de individuos con riesgo de cáncer hereditario. Se espera que el asesoramiento y el testeo genético sean incluidos en la práctica clínica diaria.

Palabras clave

Adenocarcinoma, próstata; Asesoramiento Genético; Perfil Genético; germinal; Consenso; Inhibidores de Poli(ADP-Ribosa) Polimerasas (fuente: DeCS BIREME).

INTRODUCTION

Cancer is a genetic disease in which many mutations are involved ⁽¹⁾; however, not all of these mutations are inherited in families. For example, sporadic mutations occur in tumor/somatic cells only. On the other hand, genetic cancer predisposition syndromes are often characterized by variants associated with an increased risk for certain cancers (i.e., a high penetrance phenotype) and transmission to offspring through the mother and/or father ⁽²⁾. Scientific and technological advances in genomics are revolutionizing our approach to genetic counseling, genetic testing, and target therapies, fulfilling the promise of personalized medicine ^(3,4).

Growing evidence suggests that prostate cancer (PC) has a significant inherited predisposition ⁽⁵⁾, with high risk conferred by the breast cancer susceptibility gene 1 and 2 (*BRCA1/2*), (associated with the breast and ovarian cancer genetic predisposition syndrome [HBOC]) and the homeobox B13 (*HOXB13*) (associated with hereditary prostate cancer [HPC]) ⁽⁶⁾. Inherited genetic mutations have been discovered in up to 11.8% of men with metastatic prostate cancer (mPC), primarily in deoxyribonucleic acid (DNA) repair genes such as *BRCA2* and ataxia telangiectasia mutated (*ATM*) ⁽⁷⁾. Identifying the

genetic mutations of the genetic predisposition syndrome for PC therefore has implications for the patient and their family, allowing for accuracy in the patient's treatment, family genetic counseling and is being incorporated into clinical practice guidelines.

Prostate tumors associated with germline *BRCA2* mutations often have Gleason scores greater than 8 and nodal or distant metastases at diagnosis, but these genetic variants cannot be excluded in patients without such clinicopathologic features. Germline mutations in *BRCA2* are associated with poor clinical outcomes, while the prognostic implications of heritable mutations in other DNA damage response (DDR) genes are less well established. Thirty percent of patients with metastatic prostate cancer who carry a pathogenic/likely pathogenic germline DDR variant had no previous family history of cancer. Some somatic and germline mutations in genes involved in the homologous recombination pathway are potential predictors of response to platinum-based chemotherapy and poly (ADP)-ribose polymerase inhibitors (PARPi) ⁽⁸⁾.

Most patients with hormone-sensitive PC treated with the standard of care (androgen deprivation therapy) will progress to metastatic castration-resistant prostate cancer

(mCRPC) within 2 to 3 years of diagnosis. With no curative therapies available, mCRPC remains an aggressive disease with a poor prognosis and for which better therapeutic options are needed. Two PARP inhibitors, olaparib and rucaparib, were approved by the US Food and Drug Administration (FDA) as target therapy for mCRPC^(9,10). Olaparib was approved by the FDA for patients with mCRPC with a pathogenic/likely pathogenic variant germline or somatic homologous recombination repair (HRR) gene mutations that had progressed to enzalutamide or abiraterone, based on the results of the PROfound study⁽¹⁰⁾.

Accelerated approval was granted to rucaparib in BRCA1/2 mutated mCRPC (germline or somatic) that had previously received androgen receptor-targeted therapy and taxane-based chemotherapy based on the results of the TRITON2 study⁽⁹⁾. Therefore, germline testing has substantial implications when deciding on treatment⁽¹¹⁾.

This consensus aims at providing tools for the profiling of patients with prostate adenocarcinoma and seeks to impact prevention, early detection and treatment with targeted therapies. It is important to sensitize the medical profession in the identification and suspicion of genetic alterations in these patients, reduce clinical variability in treatment and optimize timely referrals to a geneticist. The recommendations given in this consensus are not a substitute for medical judgment, they are only a support for decision making.

METHODS

The Consensus was formed by specialists in oncology and genetics (6 clinical oncologists and 1 geneticist), who work at the National Institute of Neoplastic Diseases (INEN), and was carried out following the guidelines of the "Consensus Conference on Standard Operating Procedures of the European Society of Medical Oncology (ESMO)⁽¹²⁾.

In a first virtual meeting with the panel, the questions to be answered in the consensus were drafted and voted on. The definition of the clinical questions took into account the existence of controversy in the management or lack of clear guidelines and valid evidence of the efficacy of the interventions. A total of 5 questions were defined. There was total agreement. 7/7 (100%) of the votes agreed with each of the questions.

The outcomes of questions 1, 2, 3, 5 were considered critical and the outcomes of question 4 were considered important but not critical.

A systematic search of the literature was carried out to identify the clinical practice guidelines (CPG) and

evaluate the relevance of adopting or adapting some of their recommendations. Databases consulted: PubMedD/MEDLINE (Public Medical Literature Analysis and Retrieval System Online). These searches were extended to GIN, a site that compiles CPGs. Limits: Clinical practice guidelines, published in Spanish or English, in the last 10 years. The search was supplemented in the Guidelines International Network (GIN) database.

Search strategy: Search: ("prostate neoplasms"[mh] OR ("prostate"[tw]) AND ("neoplasm*"[tw] OR "cancer"[tw] OR "carcinoma"[tw])) Filters: Practice Guideline, English, Spanish, from 2012/1/1 - 2021/12/31. The systematic search yielded a total of 179,371 references, 88,035 published in the last 10 years in any language. When filtering by clinical practice guidelines, articles in Spanish or English, 134 results were obtained. The abstracts were reviewed and 14 references were obtained for full-text review. Finally, 9 CPGs were identified that met the selection criteria for review and evaluation. The searches were performed by a bioinformatics expert. Search update date: January 2022."

The CPGs were rated by two evaluators following the Assessment of Guidelines for Research and Evaluation Instrument II (AGREE II)⁽¹³⁾. Most of the evaluated guidelines could be recommended (n=8) or recommended with modifications (n=1) for use in clinical practice. The overall assessment score of the guidelines was between 100% and 80% (for 7 guidelines), between 79- 60% (for 1 guideline) and between 50% and 59% (for 1 guideline). (Details about the evaluation of the selected CPGs in the Supplementary Appendix are available at onkoresearch.com).

All the questions posed were answered in more than one of the CPGs reviewed. Therefore, no de novo searches were performed. The CPGs that cover the questions of interest meet the desired rigor.

The titles and abstracts of the searches were reviewed by two reviewers who applied the selection criteria defined for each question independently. Once the selection was completed, it was compared for disagreement. The generic inclusion criteria taken into account were: include the target population, the intervention and the comparator of interest for each question. And the following exclusion criteria: to be written in a language other than English or Spanish.

For each question, a protocol was prepared that included: the search strategy and results, a brief review of the literature identified and its methodological quality, and the Grading of Recommendations, Assessment, Development and Evaluation (GRADE)⁽¹⁴⁾ summary table of findings to support the panel in formulating recommendations.



The quality of evidence, also referred to as confidence, reflects the degree of confidence we have that the estimate of an effect is adequate to support a recommendation. Although the quality of evidence is a continuous spectrum, GRADE⁽¹⁵⁾ proposes a classification into four categories (High, Moderate, Low and Very Low). (Details about quality of evidence can be found in the Supplementary Appendix, available at onkoresearch.com).

The GRADE⁽¹⁵⁾ methodology was also used to assess the strength and direction of the recommendations. Based on the judgment obtained on each of the aspects presented and the balance between risks and benefits, the panel formulated the recommendations according to the criteria proposed by the GRADE. (Details about GRADE can be found in the Supplementary Appendix, available at onkoresearch.com).

To generate the recommendations, two virtual meetings of four hours each were held through the Zoom[®] platform. The meetings were led by a methodological expert. All

panel members received the information to be discussed in advance of each meeting. The methodological group presented a summary of the evidence. An open discussion was established with the participation of all attendees. After drafting and adjusting the recommendation, it was submitted to a vote through the electronic voting system Google forms[®], which keeps votes anonymous. The margin to accept the recommendation after discussion was established as a vote $\geq 80\%$ of the votes of the total number of people eligible to vote in each of the questions (Table 1).

Recommendations

Question 1. *What profile of patient with prostate adenocarcinoma would be suitable for genetic counseling?*

Recommendation: Genetic counseling is recommended for any patient with prostate adenocarcinoma who is ordered to undergo genetic testing. Strong recommendation in favor. Moderate quality of evidence. Five CPGs support this recommendation⁽¹⁶⁻²⁰⁾.

Table 1. Level of agreement, by voting, of the consensus recommendations.

Question and Recommendation	Panel agreement level	
	(%)	n/N
<i>What profile of patient with prostate adenocarcinoma would be suitable for genetic counseling?</i> Genetic counseling is recommended for any patient with prostate adenocarcinoma who is ordered to undergo genetic testing.	83.3	5/6
<i>What are the criteria that a patient with prostate adenocarcinoma must meet for genetic testing to be indicated?</i> Germline testing is recommended for patients with PC and any of the following: High or very high regional or metastatic risk PC, regardless of family history; Ashkenazi Jewish ancestry; Family history of high-risk germline mutations; Intraductal/cribbiform histology; Strong family history of PC.	100	6/6
<i>What are the genes to be evaluated in patients with prostate adenocarcinoma?</i> It is suggested that all patients with prostate adenocarcinoma undergo genetic testing that includes the genes shown in table 2.	100	6/6
<i>What recommendations do clinical practice guidelines give about doing somatic testing in patients with prostate adenocarcinoma?</i> In patients with mCRPC, somatic testing for alterations in HRR pathway genes and testing for "high levels of microsatellite instability" (MSI-H) or discrepancy repair deficiency (dMMR) is recommended. In patients with mCRPC or regional PC, somatic testing for alterations in HRR pathway genes and testing for MSI-H or dMMR can be considered.	100	6/6
<i>What is the multidisciplinary team's recommendation for the therapeutic (pharmacological) management of patients with prostate adenocarcinoma who are negative, positive or inconclusive for a variant of unknown significance (VUS) for the pathway genes at either the somatic or germline level?</i> Olaparib is a treatment option for patients with mCRPC and a pathogenic/likely pathogenic variant (germline or somatic) in one of the HRR genes in: second line after a first line with abiraterone or enzalutamide independently of prior docetaxel therapy; Second line after docetaxel; In subsequent lines Rucaparib* is a treatment option in mCRPC with pathogenic/probably pathogenic BRCA1/2 variant (germline or somatic): Second line after a first line with abiraterone or enzalutamide; in second line after docetaxel; in subsequent lines. Rucaparib* can be given in patients who have not received prior taxane-based chemotherapy because they are unsuitable. *Rucaparib is not yet registered for use in prostate cancer patients in Peru. VUS result: Clinical decisions should not be based on a VUS result.	83.3	6/6

Subsequently, a draft of the final consensus document was generated, incorporating adjustments based on additional input from the panelists, socialized and sent for peer review. The meetings were audio and video recorded for later reference.

In the event of new evidence that modifies any of the recommendations of the consensus, it will be updated every three years after its publication. If there is no new evidence, it will be reviewed every three years.

Question 2. *What are the criteria that a patient with prostate adenocarcinoma must meet for genetic testing to be recommended?*

Recommendation: Germline testing is recommended for patients with PC and any of the following: High or very high regional or metastatic risk PC, regardless of family history; Ashkenazi Jewish ancestry; family history of high-risk germline mutations; intraductal/cribriform histology; strong family history of PC consisting of sibling or parent or multiple family members diagnosed with PC (non-localized) under age 60 or who died of PC.

Strong recommendation in favor. Moderate quality of evidence. Six CPGs support this recommendation ^(16-19,21,22).

Question 3. *What are the genes to be evaluated in patients with prostate adenocarcinoma?*

Recommendation: It is suggested that all patients with prostate adenocarcinoma undergo genetic testing that includes the genes listed in Table 2. In any case, it is suggested that the type of genes contained in the genetic testing panel should depend on the best available evidence at the time of sampling. Conditional (weak) recommendation in favor. Quality of evidence: moderate. Four CPGs support this recommendation ^(16,17,19,23).

Question 4. *What recommendations do clinical practice guidelines give about doing somatic testing in patients with prostate adenocarcinoma?*

Recommendation: In patients with mCRPC, somatic testing for alterations in HRR pathway genes and testing for "high levels of microsatellite instability" (MSI-H) or discrepancy repair deficiency (dMMR) is recommended. In patients with mCRPC or regional PC, somatic testing for alterations in HRR pathway genes and testing for MSI-H or dMMR may be considered. Conditional recommendation in favor. Quality of evidence: moderate. Four CPGs support this recommendation ^(16,18,21,22).

Good practice point: Tumor testing may provide information suggestive of a potential germline finding. Regardless of tumor findings, germline testing should be performed if clinically indicated (Conditional recommendation in favor. Quality of evidence: moderate). MSI-H (microsatellite instability) describes cancer cells that have a large number of mutations (in 30% or more of the microsatellites). Microsatellites are short, repeated sequences of DNA. Cancer cells with MSI-H may have a defect in the ability to correct errors when copying DNA. The dMMR (discrepancy repair deficiency) and its characteristic genetic signature, genome-wide MSI-H, define a unique biological subset of cancers characterized by a high mutational tumor burden and potential responsiveness to immunotherapy.

Table 2. Genes to be evaluated in patients with prostate adenocarcinoma

Genes to evaluate	Definition
<i>BRCA1</i>	Breast cancer susceptibility gene 1
<i>BRCA2</i>	Breast cancer susceptibility gene 2
<i>ATM</i>	Ataxia telangiectasia mutated
<i>CHECK2</i>	Checkpoint kinase 2
<i>PALB2</i>	Partner and localizer of BRCA2
<i>MLH1</i>	MutL homolog 1
<i>MSH2</i>	MutS homolog 2
<i>MSH6</i>	MutS homolog 6
<i>PMS2</i>	Post-meiotic segregation increased 2
<i>Additional genes to consider depending on the clinical context</i>	
<i>RAD51B</i>	RAD51 paralog B
<i>RAD51C</i>	RAD51 paralog C
<i>RAD51D</i>	RAD51 paralog D
<i>RAD54L</i>	RAD54 paralog L
<i>BARD1</i>	BRCA1 Associated RING Domain 1
<i>CDK12</i>	Cyclin Dependent Kinase 12
<i>CHECK1</i>	Checkpoint kinase 1
<i>FANCL</i>	FA Complementation Group L
<i>ATR</i>	Ataxia telangiectasia and Rad3-related protein
<i>NBN</i>	Nibrin
<i>GEN1</i>	Flap endonuclease GEN homolog 1
<i>EPCAM</i>	Epithelial cellular adhesion molecule
<i>MRE11A</i>	MRE11 homolog A, double-strand break repair nuclease
<i>BRIP1</i>	BRCA1 Interacting Helicase 1
<i>FAM175A</i>	FAM175A protein

Question 5. *What is the multidisciplinary team's recommendation for the therapeutic (pharmacological) management of patients with prostate adenocarcinoma who are negative, positive or inconclusive for a variant of unknown significance (VUS) for the pathway genes at either the somatic or germline level?*

Recommendation: Olaparib is a treatment option for patients with mCRPC and a pathogenic/likely pathogenic variant (germline or somatic) in one of the HRR genes in: second line after a first line with abiraterone or enzalutamide independently of prior therapy with Docetaxel; second line after Docetaxel. In subsequent lines Rucaparib* is a treatment option in mCRPC with pathogenic/likely pathogenic BRCA1/2 variant (germline or somatic) in: second line after first line with abiraterone or enzalutamide; in second line after docetaxel; in subsequent lines.

Rucaparib* can be given in patients who have not received prior taxane-based chemotherapy because they are unsuitable.

*Rucaparib is not yet registered for use in prostate cancer patients in Peru.

VUS outcome: Clinical decisions should not be based on a VUS outcome.

Strong recommendation in favor. High to moderate quality of evidence. Five CPGs support this recommendation^(16,21-24).

DISCUSSION AND CONCLUSIONS

Guidelines are limited with respect to genetic counseling and genetic testing for prostate adenocarcinoma and focus only on BRCA1/2 testing. In most advanced prostate tumors, actionable targets are identified. In very low-risk and low-risk PC patients, germline testing is recommended if there is a positive family history. For intermediate-risk patients, germline testing is recommended if there is a positive family history or intraductal/criform histology. Germline testing is always recommended in high and very high risk patients. Much progress has been made in the discovery of genes and their mutations related to the risk of genetic predisposition to cancer syndrome. This is an exponentially growing field and not all the information currently received from commercial testing panels correlates with the possibility of therapeutic intervention. However, it proves to be useful information, to assess familial cancer risk and to be able to take preventive measures. While substantial recent advances have been made, there are many unmet needs in the approach and management of prostate cancer. Somatic and germline mutations in homologous recombination repair (HRR) genes may predict the clinical benefit of PARPi.

Translating recommendations into decisions made in clinical settings involves processes aimed at modifying the behavior of users of consensus recommendations. Healthcare providers and patients will follow the recommendations contained therein if they are adequately aware of them and have the ability to apply them. In the context of the implementation of the consensus, the main barriers to the application of the recommendations have been identified as follows: restrictions for patients in access to health services, either due to lack of timely care, delays in authorizations, failures in affiliation, economic restrictions or ability to pay, denial of authorizations or refusals to provide services and medicines; lack of knowledge about genetic profiling of patients with prostate adenocarcinoma by the first level of care and little agility for the process of referral and counter-referral between related specialties.

Among the interventions aimed at overcoming barriers, the following are proposed: distribution of printed and/or digital educational materials; academic training activities with the participation of local opinion leaders; socialization activities with the participation of patients; dissemination

in the mass media; written materials in national scientific journals; and coordination with national health authorities to implement the consensus recommendations.

Finally, we will seek to define a follow-up and evaluation plan for the process of implementing the recommendations, which will make it possible to evaluate the impact on the outcomes of patients with prostate adenocarcinoma in the country by generalizing genetic profiling.

Limitations of this consensus

The accelerated appearance of new markers of clinical interest in the pathologies treated by this consensus could in the short to medium term modify some of the recommendations and the appearance of new target therapies could change the recommendations in one direction or another. The literature search was limited to PubMed and supplemented in GIN. The primary evidence on which the CPGs are based was not used, although the CPGs were graded using the AGREE II instrument. Since this is an expert consensus, and despite being based on evidence, the risk of subjectivity in the opinions is always implicit.

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Supplementary Appendix

Additional information about this article is available in the Supplementary Appendix.

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