UKCGG/CStAG statement on extension of testing undertaken under R444.1 to include *PALB2*

Background

In the National Genomic Test Directory (NGTD) for Rare and Inherited Disease, testing under indications R208 (Inherited breast cancer and ovarian cancer) and R430 (Inherited prostate cancer) is restricted to individuals in whom the *a priori* probability of identifying a germline pathogenic variant (GPV) on panel testing is estimated to be approximately 10% or higher, based on their personal and family history of breast or prostate and related cancers. R208 includes testing of *BRCA1, BRCA2*, *PALB2, ATM, CHEK2, RAD51C* and *RAD51D*, and R430 includes *BRCA1, BRCA*2, *PALB2, ATM, CHEK2, MLH1, MSH2* and *MSH6*.

Prompted by changes in eligibility criteria for use of Olaparib[1], indication R444 (NICE approved PARP inhibitor treatment) was created in June 2023 (V5.2), to define criteria for germline genetic testing for patients with breast (R444.1) or prostate (R444.2) cancer not otherwise meeting criteria for testing under R208/R430. At that time, test targets for R444.1 aligned with those of R208 (*BRCA1, BRCA2, PALB2, ATM, CHEK2, RAD51C, RAD51D*), while test targets for R444.2 were restricted to *BRCA1* and *BRCA2*. The rationale for aligning R208 and R444.1 was in recognition of overlapping eligibility between the two indications, existing laboratory pipelines and to minimise referrals for retrospective reanalysis if referrers later realised that they had requested restricted testing via R444.1 for R208-eligible patients in error.

Further to changes in eligibility for use of Talazoparib in patients with breast cancer, R444.1 was amended (NTD v7, July 2024), to include additional criteria for testing aligning with treatment eligibility, and to restrict targets for testing to *BRCA1* and *BRCA2*, to align with R444.2 and reflect only the targets relevant to the treatments for which the test was commissioned. The rationale cited for restriction of targets tested under R444.2 included concerns from GLHs raised during contracting and commissioning discussions, regarding capacity, increasing numbers of referrals due to the broader eligibility criteria for Talazoparib, and the recommended 21-day turnaround time.

Following publication of NTD v7, informal discussions via email and through CStAG (CanVIG steering and advisory group) meetings were undertaken to determine real world application of the update. These discussions indicated that most GLHs were continuing to analyse all R208 targets for R444.1 requests rather than enacting restriction of testing, to minimise work in revising laboratory workflows, in anticipation of requests for reanalysis of other R208 targets, and because of concerns related to communication of changes in test targets to referring mainstream clinicians. However, a minority of GLHs had gone to great efforts to revise laboratory processes to adhere to the test directory as written, leading to inequitable and inconsistent practice nationally.

UKCGG/CanVIG-UK Recommended Amendment to R444 test targets

R444.1: We recommend that test targets for R444.1 include *BRCA1*, *BRCA2* and *PALB2*.

R444.2: At the present time, we do not support the inclusion of targets other than *BRCA1/BRCA2* under R444.2, given that the association between prostate cancer and constitutional pathogenic variants in *PALB2* is unclear and identification of such a variant will not, at present, influence treatment options. Where patients with prostate cancer have a strong family history of breast cancer, their affected relatives may seek referral to their local regional genetics service to determine eligibility for R208 testing.

We do not, at this time, support inclusion of *ATM, CHEK2, RAD51C* or *RAD51D* under either indication.

Rationale for amendment

Laboratory workload in variant interpretation and freeing up capacity to increase number of tests in response to increasing numbers of referrals are important considerations in test targets. We support inclusion of testing targets associated with the highest clinical utility – namely variants conferring PARP inhibitor treatment eligibility **and** those associated with highest cancer risk[2].

The majority of constitutional pathogenic variants in *PALB2* are associated with a high lifetime breast cancer risk as well as an increased risk of other cancers[3]. Despite its role in Homologous Recombination Repair, identification of a constitutional pathogenic variant in *PALB2* is not, at the present time, relevant for determining eligibility for PARP inhibitor treatment. However, testing of

PALB2 is associated with high clinical utility, given the high associated cancer risks and cost-effective risk-reducing interventions that could be enacted for presymptomatic carrier relatives.

Constitutional pathogenic variants in *ATM, CHEK2, RAD51C* and *RAD51D* are associated with low-moderate breast cancer risk, with risk dependent on variant type, family history and other co-existing genetic, lifestyle or reproductive modifiers of disease[4567].

Outside of the context of a significant family history, identification of a low-moderate risk susceptibility allele that does not confer PARP inhibitor eligibility has limited clinical utility. We are supportive of testing *ATM, CHEK2, RAD51C* or *RAD51D* in individuals who are eligible for testing of these genes under the R208 indication.

Referrals for retrospective reanalysis of other targets

Where R444.1 (including *PALB2*) has been undertaken, it is not necessary to undertake retrospective reanalysis of other R208 targets (*ATM, CHEK2, RAD51C* or *RAD51D*) for patients later recognised to be eligible for R208 testing unless CanRisk-estimated probability of identifying pathogenic variant **in those four genes** is estimated to be 10% or higher after considering uninformative *BRCA1, BRCA2* and *PALB2* result. Relatives of patients with an uninformative R444.1 result should be independently assessed for their own lifetime cancer risks and test eligibility according to the NGTD and offered moderate or high-risk breast cancer screening and other risk management advice based on their family history of cancer and estimated lifetime cancer risk, in line with current guidelines.

Summary and recommendations

- **We recommend that patients tested under R444.1 receive germline genetic testing of *BRCA1, BRCA2* AND *PALB2*.**
- Retrospective reanalysis of *ATM, CHEK2, RAD51C* and *RAD51D* should not be routinely undertaken for patients with an uninformative R444.1 result.
- Clinical genetics and laboratory services should liaise with local clinicians ordering R444.1 and R208 in the mainstream context to emphasise differences in eligibility criteria and test targets and highlight that patients eligible for R208 should have this as a first line test, even if eligible for R444.1. In this instance, the referring mainstream clinicians should be encouraged to flag clinical urgency and impact of test result to the testing laboratory.

Note

This change cannot, at the present time, be reflected in the wording of the national genomic test directory or PanelApp, given that the indications must align with current treatment eligibility.

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[1] NHS England » Cancer Drugs Fund https://www.england.nhs.uk/cancer/cdf/

[2] Badrick T, Bowling F. Clinical utility - Information about the usefulness of tests. Clin Biochem. 2023 Nov;121-122:110656. doi: 10.1016/j.clinbiochem.2023.110656. Epub 2023 Oct 4. PMID: 37802380.

[3] Yang X, Leslie G, et al. Cancer Risks Associated With Germline *PALB2* Pathogenic Variants: An International Study of 524 Families. J Clin Oncol. 2020 Mar 1;38(7):674-685. doi: 10.1200/JCO.19.01907. Epub 2019 Dec 16. PMID: 31841383; PMCID: PMC7049229.

[4] Pal T, Schon KR, et al ACMG Professional Practice and Guidelines Committee. Electronic address: documents@acmg.net. Management of individuals with heterozygous germline pathogenic variants in ATM: A clinical practice resource of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2025 Jan;27(1):101243. doi: 10.1016/j.gim.2024.101243. Epub 2024 Dec 5. PMID: 39636577.

[5] Adank MA, Verhoef S, et al Excess breast cancer risk in first degree relatives of CHEK2∗1100delC positive familial breast cancer cases. Eur J Cancer. 2013 May;49(8):1993-9. doi: 10.1016/j.ejca.2013.01.009. Epub 2013 Feb 14. PMID: 23415889.

[6] Breast Cancer Association Consortium; Dorling L, Carvalho S,Et al Breast Cancer Risk Genes - Association Analysis in More than 113,000 Women. N Engl J Med. 2021 Feb 4;384(5):428-439. doi: 10.1056/NEJMoa1913948. Epub 2021 Jan 20. PMID: 33471991; PMCID: PMC7611105.

[7] Yang X, Song H, et al. Ovarian and Breast Cancer Risks Associated With Pathogenic Variants in RAD51C and RAD51D. J Natl Cancer Inst. 2020 Dec 14;112(12):1242-1250. doi: 10.1093/jnci/djaa030. PMID: 32107557; PMCID: PMC7735771.