Germline Genetic Testing for Pancreatic Cancer

Frequently Asked Questions – for healthcare professionals

1. What genes are included on R367?

BRCA2, PALB2, CDKN2A

However, this may change as we learn more about inherited causes of pancreatic cancer this may change. Please ask clinical genetics for advice if you are uncertain.

2. What is the rationale for offering genetic testing to patients with pancreatic cancer?

Although the majority of cases of pancreatic cancer are sporadic (not due to 'high risk' inherited genes), up to one in 10 pancreatic cancers occur in the setting of a hereditary cancer predisposition syndrome [1, 2].

Prospective studies of patients with pancreatic ductal adenocarcinoma, unselected for age of diagnosis, ethnicity and family history, identified germline pathogenic variants in, *BRCA2* in 1.3-2.1% [3-6] and *PALB2* in 0.3-0.8% [3-5].

For patients with pancreatic cancer with a personal or family history of related cancers like breast, ovarian cancer or melanoma, germline pathogenic variants were identified in a higher proportion: *BRCA2* in 3.3-17.2% [7-13] and *PALB2* in 0.6-2.1% [8, 9, 14].

Determining if a patient carries a germline pathogenic variant in these genes has important therapeutic implications. *BRCA1* and *BRCA2* are key proteins involved in repair of double-stranded breaks in the DNA, by a process called homologous recombination, [15, 16]. *PALB2* is an essential regulator of *BRCA2* function [17]. Loss of function of these genes due to pathogenic variants leads to homologous recombination deficiency (HRD). Because of the inability to effectively repair double-strand DNA breaks, HRD-deficient tumours are particularly sensitive to DNA damaging and cross-linking agents, [18, 19] such as the platinum chemotherapies, leading to improved survival [20, 21]. Patients with HRD pancreatic tumours may also benefit from a new class of drugs known as PARP inhibitors [22, 23], which are not currently licensed by the National Institute of Clinical Excellence (NICE) but may be available on a trial basis.

CDKN2A is a gene predominantly associated with predisposition to melanoma and pancreatic cancer[3,4].

Identifying a germline pathogenic variant in *BRCA2, PALB2 or CDKN2A* may have implications for the patient's future cancer risk, and also for their relatives, allowing access to predictive genetic testing and cancer screening and prevention measures (e.g. for breast cancer).

3. Why is asking about a patient's ethnicity or ancestry relevant?

Patients with pancreatic cancer from Ashkenazi Jewish ethnic backgrounds had a much higher chance of carrying a pathogenic variant in *BRCA2* (around 3.6-15.6%) [7, 24-30] due to the high rate of 'founder' mutations in this gene in this population. Similarly, patients with pancreatic cancer who are of French-Canadian ancestry had a higher chance of carrying a pathogenic variant in *PALB2*, around 1.3% [24].

4. Which patients with pancreatic cancer are eligible for genetic testing?

The National Genomic Test Directory indicate the eligibility criteria under code **R367** (available at https://www.england.nhs.uk/wp-content/uploads/2018/08/Rare-and-Inherited-Disease-Eligibility-Criteria-November-2020-21.pdf). For the directory dated Nov 2020_2011, the eligibility criteria are;

1. Patients with pancreatic cancer age <60, OR

2. Patients with pancreatic cancer age <70, AND

a. Personal history of breast cancer age <60, melanoma age <60, OR ovarian cancer, OR

b. One first / second degree relative with pancreatic cancer age <60, OR

c. Two first / second degree relatives with any of breast cancer age <60, melanoma age <60, OR ovarian cancer

Eligibility criteria for genetic testing may change over time.

5. How do I explain *BRCA2, PALB2* and *CDKN2A* genetic testing to patients?

Below is a suggested brief step-by-step outline in plain English which outlines the key points about genetic testing to explain to patients:

a) The genetic test is a blood test

b) It will check whether you have a fault in three genes called BRCA2, PALB2 and CDKN2A.

c) For most patients without a family history of cancer, the result is normal (no faults are found). This is reassuring for your family members as it means your cancer is less likely to be hereditary.

d) About 5-10% patients with pancreatic cancer have a fault in BRCA2, PALB2 and CDKN2A. If this happens it may help guide your cancer treatment. It will also mean your relatives could also inherit the same faulty gene and they would be able to have a blood test too to find out if they have any increased cancer risks.

e) Some test results give an uncertain result, i.e. a variant of uncertain significance. This means it's not clear if your gene is faulty or not.

f) If the result identifies a fault in one of the genes tested then you will be referred to the genetics team for further discussion about the implications of this results for you and your family. There is also a leaflet you can take home today which explains this more.

6. Why do I need to check family cancer history information?

If there is a family history of other cancers, referral to the cancer genetics team may still be appropriate, even if the genetic test result are normal to assess whether there is any additional genetic testing or cancer screening recommended in the family. See Question 13 for more information.

7. What happens once my patient has had blood taken for genetic testing?

The blood sample will be sent directly to the lab and the result will be returned to the requesting clinician. If you would also like to refer the patient to the cancer genetics team, due to their family history or because the patient has further questions, please make a referral via cancergenetics.stg@nhs.net. Please ensure you provide correct patient contact details with referral. If your patient requires an interpreter or is not suitable for a telephone appointment, please mention this in your referral.

8. What is the turnaround time for receiving results?

Results turnaround time for rapid testing is approximately 4-8 weeks from receipt of blood sample. Occasionally there are unavoidable delays from the laboratory. If the result is required more urgently for treatment then please make this clear on the blood test request form.

9. What are the possible results of genetic testing?

There are three outcomes of genetic testing:

1. A pathogenic variant is detected in *BRCA2, PALB2 or CDKN2A*: This is a clinically actionable result. The patient may be eligible to consider PARP inhibitor therapy and their relatives are able to access predictive genetic testing via referral to their local clinical genetics service. **All patients with this result should be referred to the Cancer Genetics team to discuss the implications further** and are added to our 'Carrier Register' to ensure they are contacted about relevant updates in future.

2. No pathogenic variants are detected in *BRCA2, PALB2 or CDKN2A*: This is a normal result. The reason why this patient developed cancer remains unknown. It is still possible there may be a genetic contribution to their disease due to variant/s in other gene/s. Additional genetic testing may be offered based on the family history (see Question 12). Predictive genetic testing is not available for relatives and they are less likely to have a high risk of developing cancer, though this will be assessed by the clinical genetics team based on family history.

3. A variant of uncertain significance (VUS) is detected: This is not a clinically actionable result. A variant has been detected in the patient's *BRCA2, PALB2 or CDKN2A* gene, but it is not clear if this variant is disease-causing (i.e. pathogenic) or is just natural, benign variation. As such, it cannot be used to inform treatment or risk for family members at the present time. Predictive genetic testing is

not available for family members. **We would recommend patients with a VUS are referred to Cancer Genetics for further discussion** about any additional investigations that can be performed in the family to clarify the significance of the VUS.

10. What tubes should blood be collected in for genetic testing?

4-8mls of blood should be collected in EDTA (purple top) tubes.

Please send the blood sample with the completed *"GLH non-WGS form" (available via website* https://www.stgeorges.nhs.uk/service/specialist-medicine/clinical-genetics/clinical-genetics/cancer-genetics/*) to*

Viapath Genetics Lab, Genetics Department Tower Wing - 5th Floor Guy's Hospital Great Maze Pond London SE1 9RT

All samples should be sent by first class post, courier, hospital transport or taxi.

On receipt of the blood sample the laboratory will activate the sample if the R number and eligibility criteria for genetic testing are clearly stated.

11. What should I advise patients with regards to their future cancer risk if they are found to have a hereditary cause for their pancreatic cancer?

Patients who are found to have a pathogenic variant in *BRCA2, PALB2 or CDKN2A* should be referred to Cancer Genetics for further discussion.

Women who are found to carry a *BRCA2 or PALB2* pathogenic variant have an increased lifetime risk of developing breast cancer and ovarian cancer. Those who are found to carry a CDKN2A pathogenic variant have an increased lifetime risk of melanoma. However, for patients who already have a diagnosis of pancreatic cancer the risk of disease progression/ relapse is often greater than the remaining lifetime risk of developing a second cancer. As such, decisions around breast screening should be made in the context of the patient's pancreatic cancer prognosis. In most cases, this means breast screening is not implemented, but it should be considered for patients in remission.

For those who do have breast screening, the current breast screening guidelines for female BRCA2 and *PALB2* carriers are:

- Age 30-50: annual breast MRI
- Age 40-70: annual mammogram and review frequency after 70.

Alternatively, some women consider risk reducing bilateral mastectomy.

Screening for ovarian cancer is not effective, and therefore female BRCA gene carriers are advised to consider risk-reducing surgery to remove their ovaries and fallopian tubes (bilateral salpingo-oophorectomy) once they have completed their families. PALB2 carriers have a lower risk of ovarian cancer as so their management will be guided by family history assessment.

Dermatology review is recommended for people who carry CDKN2A pathogenic varaints.

12. Who will inform the patient of their genetic test results?

The results will be returned to the requesting clinician , who will be responsible of informing the patient of their results and making onward referrals as appropriate.

All patients with a positive result (pathogenic variant detected) or a VUS should be referred to clinical genetics.

13. Will any other genes be tested?

Currently, only *BRCA2*, *PALB2 and CDKN2A* testing will be requested. The panel may be updated in the future to include other genes linked to pancreatic cancer. For example, this panel does not currently include genes associate with Lynch syndrome. If there is a family history of Lynch syndrome-related cancers (i.e. bowel, endometrial, small bowel, gastric, brain, ureter, renal pelvis, hepatobiliary and pancreatic cancers), please ensure the patient has been referred to Cancer Genetics.

All additional investigations will be ordered by the genetics team in consultation with the patient. The turnaround time for receiving results for these additional genetic tests will be longer as they don't currently impact management.

14. Further questions?

Please contact the Cancer Genetics Team via email at cancergenetics.stg@nhs.net. You can also reach us by telephone 9am-5pm Monday to Friday at 020 8725 5333 or 077 8784 3070.

ADDITIONAL INFORMATION - Studies on germline mutation prevalence

PDAC – pancreatic ductal adenocarcinoma
AJ – Ashkenazi Jewish
FDR – first degree relative
SDR – second degree relative
TDR – third degree relative
CPG – cancer predisposition gene

Study	N=PDAC	*BRCA1*	*BRCA2*	*PALB2*	Notes
Brand et al 2018 [3]	298	4/298 (1.3%)	4/298 (1.3%)	1/298 (0.3%)	Prospective, Unselected by family history, sequenced 32 CPGs; 9% AJ nearly 20% of the patients had a personal history of at least 1 other cancer
Hu et al 2018 [4]	3030	0.6% of cases and 0.2% of controls; OR, 2.58; 95% CI, 1.54-4.05	1.9% of cases and 0.3% of controls; OR, 6.20; 95% CI, 4.62-8.17	0.4% cases; 95% CI, 0.20%-0.69%, (not significant)	Case control study: 3030 adults in Mayo clinic pancreas cancer registry sequenced for 21 CPGs vs 123136 GnomAD controls 5.5% of cases had an additional personal history of breast, ovarian, colorectal, or non-ovarian gynaecologic cancers 11.3% of patients had a family history (FDR and SDR) of pancreatic cancer
Smith et al 2018 [24]	150 F-C	0	6/150 (4%)	2/150 (1.3%)	150 French-Canandians had founder testing
		0	2/114 (1.8%)	0	114/150 had full gene testing
	236 Toronto	1/30 AJ (3.3%)	2/30 AJ (6.7%)	0	236 Montreal-Toronto study, 30 AJ founder
		1/206 (0.5%)	6/206 (2.9%)	0	206 non-founder testing
Mandelker et al 2017 [25]	176	6/176 (3.4%)	11/176 (6.25%)	1/176 (0.6%)	patients with advanced (Stage 3-4) cancer at Memorial Sloan Kettering Cancer, 76 germline CPGs sequenced, included many AJ 176 pancreatic cancer patients (16.9% of cohort), of which 132 tested negative for 72 gene panel and 44 mutation positive
Shindo et al 2017 [5]	854	3/854 (0.4%)	12/854 (1.4%)	2/854 (0.8%)	Germline sequencing of 32 CPGs in 854 PDAC patients
Hu et al 2016 [6]	96	1/96 (1.0%)	2/96 (2.1%)	0	96 patients unselected for a family history of cancer who were recruited to the Mayo Clinic Pancreatic Cancer patient registry over a 12-month period, screened for 22 CPGs, no AJ patients
Grant et al 2015 [31]	290	1/290 (0.3%)	2/290 (0.6%)	0	290 probands from 3 strata, based on family history of breast and/or ovarian cancer, pancreatic cancer, or neither. Included those with known mutations.

					39/290 (13.9%) had pancreatic cancer in FDR
Holter et al 2015 [7]	306	3/306 (1%)	11/306 (3.6%)	0/79 (then discontinued)	Unselected, consecutive, prospective incident patients with pancreatic ductal adenocarcinoma were recruited at a single cancer centre over a 2-year period 37/306 (12.1%) reported a family history of PDAC in FDR, SDR or TDR 33/306 (10.8%) patients AJ - 12.1% founder mutation prevalence among AJ patients, whereas the prevalence among non-AJ patients was 3.7%. 5 BRCA carriers had previous cancer
Zhen et al 2015 [8]	727	6/716 (0.8%)	25/716 (3.5%)	4/716 (0.6%)	Sampled from multicenter Pancreatic Cancer Genetic Epidemiology (PACGENE) Consortium of 2,853 unrelated kindreds containing at least two family members affected with pancreatic cancer 521/727 met criteria for familial pancreatic cancer ie. at least two affected FDRs; remaining 206/727 were non-FPC cases (at least two affected biologic relatives, but no FDR). A small proportion (1.2%) of the total sample also had a personal history of melanoma; among females, personal history of breast and ovarian cancers occurred in 6.4 and 0.6%, respectively. 43 (8.0%) were of AJ descent among the 538 who self-reported this information Not all deletions and duplications were comprehensively tested for in BRCA1 and BRCA2. Also, duplications and deletions were not tested for in PALB2
Salo-Mullen et al 2015 [9]	151	4/151 (2.6%)	13/151 (8.6%)	1/48 (2.1%)	175 consecutive patients with PAC who underwent clinical genetics assessment at Memorial Sloan Kettering Cancer Center between 2011 and 2014, enriched for AJ Enriched for multiple primaries – 46/175 (26.2%) patients with more than one primary malignancy *PALB2* germline genetic evaluation was considered in light of a personal and/or

					family history of pancreatic and breast cancer
Lucas et al 2014 [26]	32	2/32 (6.25%)	5/32 (15.6%)	Not done	26/32 (81.3%) Ashkenazi Jewish PDAC The diagnostic yield was 7/32, or 21.8%. The diagnostic yield for the Ashkenazi Jewish PDAC cohort alone was 5/26, or 19.2%.
Lucas et al 2013 [27]	37 (AJ and PDAC)	4/37 (10.8%)	4/37 (10.8%)	Not done	single-site study of patients who underwent surgical pancreatic tumor resection and self-identified as Ashkenazi Jewish (retrospective) between 2003-2011 94.3% had no prior history of breast or ovarian cancers
Blanco et al 2013 [14]	132	Not done	Not done	2/132 (1.5%)	132 non-BRCA1/BRCA2 unrelated breast/ovarian cancer families with a personal history of both breast and pancreatic cancer, or a family history with pancreatic cancer cases. PALB2 sequencing and MLPA
Ferrone et al 2009 [28]	145	2/145 (1.3%)	6/145 (4.1%)	Not done	Unselected self-reported Jewish patients with pancreatic adenocarcinoma resected between January 1986 and January 2004 A previous cancer was reported by 24% Enriched for AJ, previous cancer and only operated patients
Couch et al 2007 [11]	151 families	Not done	5/151 (3.3%)	Not done	Affected probands from 151 high-risk families o 41 families Mayo clinic – no AJ o 101 families Johns Hopkins - minimum of two second-degree relatives with pancreatic cancer, 10 AJ o 9 families Toronto – one AJ Only mutations that result in truncation of the BRCA2 gene were categorized as deleterious. Enriched for familial cases - 118 had two or more FDR and SDR with pancreatic cancer, and an additional 33 had two or more affected second-degree relatives. Also did analysis combined with 29 families from Murphy et al 2002. BRCA2 truncating mutations seen in 10/180 (6%) families
Hahn et al 2003 [12]	26 families	Not done	3/26 (11.5%)	Not done	26 European families (64 individuals) in which at least two FDRs had a histologically confirmed diagnosis of pancreatic ductal adenocarcinoma. All white, no AJ, none fulfilled criteria for hereditary tumour

					syndromes, only BRCA2 sequenced by truncation
Murphy et al 2002 [13]	29 families	Not done	5/29 (17.2%)	Not done	Familial pancreatic cancers – 3 or more family members with pancreatic cancer, at least two of which were FDR (and did not satisfy criteria for other hereditary cancer syndromes) 6/29 AJ – three of 5 mutation carriers had AJ founder mutations
Lal et al 2000 [10]	38	1/38 (2.6%)	3/38 (7.9%)	Not done	102 patients with newly diagnosed pancreatic adenocarcinoma, unselected for age, sex, family history, or ethnic origin (Toronto, Canada) Families classified as high risk/familial, intermediate risk/familial, intermediate risk/non-familial, or low risk according to defined criteria. Only 38 High- and intermediate-risk cases were analyzed for germline mutations Fourteen of 102 (14%) patients reported that they were of AJ descent. All mutations were in AJ patients Used PTT/ heteroduplex methods only (truncating mutations)
Ozcelik et al 1997 [29]	41	Not done	2/41 (4.9%)	Not done	Unselected pancreatic cancer patients, 13 AJ Subsequently analyzed 39 AJ patients with pancreatic cancer and found BRCA2 6174delT mutations in 4/39 (10%) patients
Goggins et al 1996 [30]	41	Not done	3/41 (7.3%)	Not done	41 adenocarcinomas of the pancreas (30 pancreatic adenocarcinoma xenografts and 11 pancreatic cancer cell line); Truncation assay only

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