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## **Genetic Counselling Referral Practices for Patients with Pancreatic Adenocarcinoma: A French Retrospective Multicentre Observational Cohort Study (CAPANCOGEN)**

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## **Abstract (241/250 words)**

### **Background/objectives**

Genetic counselling (GC) is a key step in the identification of inherited germline mutations. However, the oncogenetic practices are poorly described for pancreatic adenocarcinoma (PA) in Europe. The CAPANCOGEN study aimed to describe the GC referral practices in France and assess the implementation of international guidelines in patients with PA.

### **Methods**

Information about GC referrals with PA was collected in 13 French centres from September 2019 to October 2021. In the 5 largest centres, personal and familial histories of cancers and diseases associated with a higher risk of germline mutations were collected in 460 patients, according to international, American, European and French GC referral guidelines. Univariate and multivariate logistic regression analysis were performed to identify the factors influencing GC referral.

### **Results**

Among 833 patients, a total of 100 patients (12%) had an indication of GC according to local multidisciplinary tumour board meetings (MTBM). Among these patients, 41% did not undergo GC. The median time between MTBM and GC was 55 days (IQR: 14.5-112). Among 460 patients with collected personal and familial history, 31.5% were not referred to a GC despite an existing indication. In multivariate logistic regression analysis, suspected *CDKN2A* ( $p=0.032$ ) or *BRCA* mutation ( $p<0.001$ ),

familial pancreatic cancer history ( $p < 0.001$ ) and controlled disease with first-line platinum-based chemotherapy ( $p < 0.001$ ) increased the referral rate. Conversely, older age ( $p = 0.002$ ) and a locally advanced PA ( $p = 0.045$ ) decreased the risk of GC referral.

## **Conclusions**

GC referral is inadequate despite valuable information in patients' medical files.

## **Keywords**

Pancreatic Neoplasms, Genetic counselling, Genetic testing, Genetic Predisposition to Disease, Germline Mutation.

## **Abbreviations:**

PA: Pancreatic Adenocarcinoma,

FPC: Familial Pancreatic Cancer,

HBOC: Hereditary Breast and Ovarian Cancer

FAMMM: Familial Atypical Multiple Mole Melanoma

GC: genetic counselling

MTBM: Multidisciplinary Tumour Board Meeting,

PARP: poly (ADP-ribose) polymérase

TNCD: *Thésaurus National de Cancérologie Digestive*

EUROPAC: European registry of familial pancreatic cancer and hereditary pancreatitis

CAPS: International of the Pancreas Screening Consortium

ACG: American College of Gastroenterology

PS: performance status

IQR: Interquartile range

NCCN: National Comprehensive Cancer Network

## Introduction

Pancreatic adenocarcinoma (PA) has a globally growing incidence with little therapeutic progress in the last decades [1–4]. PA risk factors include age, gender, cigarette smoking, obesity, chronic pancreatitis, diabetes and familial history [5,6].

Familial pancreatic cancer (FPC) is defined as an aggregation of PA (with or without germline mutations) with the occurrence of two PA or more for the first-degree relatives or three PA or more in the same family branch regardless of the degree [7]. It accounts for 5 to 10% of PA cases and a germline mutation is identified in less than 30% of the cases [7,8]. Inherited germline mutations can increase the risk of PA from 2 to 130 times compared to non-carriers. They mainly include Hereditary Breast and Ovarian Cancer (HBOC) syndrome (mostly due to *BRCA1/2* and *PALB2* mutation), Familial Atypical Multiple Mole Melanoma (FAMMM) syndrome (*CDKN2A* mutation) or Lynch syndrome (*MMR* genes mutation) [7,9–14].

In Europe, potential candidates for germline testing are identified using their familial history and can be referred to genetic counselling (GC). Germline mutation identification can have consequences for patients with a PA. First, since 2020, olaparib has been approved in Europe as a continuing treatment of *BRCA*-related metastatic PA with a response or a stable disease after at least 4 months of platinum-based first-line chemotherapy [15,16]. Also, genetic mutation identification can have consequences for healthy individuals who can be referred to a screening centre, depending on other factors [17,18]. National and international societies issued guidelines to help physicians adequately refer patients to GC and target genetic testing towards patients with a relevant personal or familial history of cancer [7,17–20]. The assessment of the implementation of a guideline is a key step in its quality evaluation and reflects its relevance, dissemination, understanding and means at

disposal to enhance patient management. However, no study has assessed the use and application of targeted genetic mutation screening guidelines in patients with PA. The CAPANCOGEN study aimed to describe the oncogenetic counselling referral practices in France, according to current guidelines, for PA and identify factors associated with GC referral.

## **Material and methods**

### **Study design**

The CAPANCOGEN study is an ancillary retrospective multicentre observational study of the original CAPANCOVID cohort [21]. This cohort involved 13 French institutions including 11 tertiary health centres and 2 secondary health centres. Participating centres included all consecutive patients over 18 years diagnosed with a PA between September 1<sup>st</sup>, 2019, and October 31<sup>st</sup>, 2020. All included patients had been discussed in multidisciplinary tumour board meetings (MTBM).

### **Data collection**

Most data had already been collected prospectively from medical records in the CAPANCOVID study [21]. Collected data about GC included the date of consultation when existing, its priority degree, and the date of the consultation for the delivery of the results. According to the French guidelines, a GC consultation should be performed quickly when the results can have a potential therapeutic consequence (anti-poly[ADP-ribose] polymerase [PARP] prescription, inclusion in a trial...) and/or especially in patients with a short life expectancy [22].

We performed additional data collection for the purpose of the CAPANCOGEN study for the patients included in the 5 largest participating CAPANCOVID centres (Reims

University Hospital, Reims Cancer Institute, Lille University Hospital, Poitiers University Hospital and Saint Etienne University Hospital). As a gold standard, we merged different guidelines including the French *Thesaurus National de Cancérologie Digestive* (TNCD) and the European registry of familial pancreatic cancer and hereditary pancreatitis (EUROPAC) guidelines to identify patients who had an indication to be screened for *CDKN2A*, *BRCA1/2*, *PALB2*, and *MMR* gene (*MLH1*, *MSH2*, *MSH6*, *PMS2*) mutations regarding their personal and familial history [7,20]. *In extenso*, we also used the International Cancer of the Pancreas Screening consortium (CAPS) and the American College of Gastroenterology (ACG) guidelines, due to their comprehensiveness [17–19]. The CAPS guidelines were initially established to identify healthy high-risk individuals and formally define the indications of PA screening [17,18]. As genetic testing should aim for high-level clinical consequences for patients' relatives in terms of early diagnosis, the use of the guidelines seemed appropriate to identify potential mutation carriers in the family. It is worth noting that Peutz Jeghers (*STK11* mutation), Li-Fraumeni syndrome (*p53* mutation) and Familial Adenomatous Polyposis (*APC* mutation) are not included as they are mostly symptomatic earlier with other diseases and, therefore, rarely part of the screening genetic panels proposed in French laboratories. The FPC criteria were also considered, as internationally defined: two or more first-degree relatives with PA or three PA or more in the same family branch regardless of the degree [7,17,19,20]. Finally, two less consensual additional criteria were added: a partial response or stable (controlled) metastatic disease using platinum-based first-line chemotherapy at first evaluation, and an age inferior to 50 years at diagnosis. One patient could have several indications to be referred to a GC. All of these criteria are summarised in **Supplementary Table 1**. The criteria for GC in Supplementary Table 1 are a

synthesis of the guidelines and are not explicitly available as so in the French guidelines. This synthesis was not given to each inclusion centre as this real-world observational study aims to evaluate common practices without intervention. The referral to a genetic counsellor was left to each physician discretion, depending on the context.

### **Objectives and endpoints**

The main objective was to describe the GC referral practices in France in the entire CAPANCOVID cohort. The primary endpoints included the number of patients with an indication of referral to GC according to the local MTBM and the GC consultation conversion rate (GC consultation performed/GC consultation indicated).

The secondary objectives were to assess the implementation of national and international GC referral guidelines and to identify associated factors with GC referral in patients diagnosed with PA. The secondary endpoints included the adequacy and mismatch rate according to the prespecified gold standard for a GC referral. The adequacy rate was defined as the rate of rightfully performed or unperformed oncogenetic consultation according to our gold standard ( $n_{\text{performed/indicated}} + n_{\text{not performed/not indicated}}/N$ ). The mismatch rate was defined as the rate of wrongfully performed or unperformed according to the same gold standard ( $n_{\text{not performed/indicated}} + n_{\text{performed/not indicated}}/N$ ). Baseline characteristics were then compared in the two groups of patients (rightfully performed versus wrongfully missed) to identify the factors associated with GC referral in patients with PA in our ancillary cohort.

### **Statistical analysis plan**

Data were presented as medians and interquartile range (IQR) for continuous variables and counts and frequencies (percentage) for categorical variables. Data were then compared using the Chi-square and Wilcoxon test. The subcohort characteristics were visually compared to the initial cohort, without additional statistical tests. A univariate and multivariate logistic regression was performed to compare the baseline characteristics of patients with wrongfully unperformed GC according to the specified criteria, versus the rest of the patients. The outcome variable was wrongfully unperformed GC referrals. The reference category was a missed consultation. The covariates included in the multivariate analysis were chosen upon clinical relevance [age (as a continuous variable), sex, performance status (PS), disease stage, first-line treatment, distance from home to treatment centre, suspected germline mutation, FPC criteria, platinum-based chemotherapy sensitivity]. As the CAPS A3 and FPC, and PALB2 and BRCA criteria are similar, only BRCA and FPC criteria were kept in the model to avoid any collinearity hampering the interpretation. The reference strata for multifactorial variables were the earlier stage of PA (resectable disease), the surgical treatment and the absence of clinical characteristics. The null and residual deviance were compared using an ANOVA test to assess the prediction of the model. Additional sensitivity analyses were performed comparing multiple fits, using <50 versus  $\geq$ 50 years threshold, and aggregated PS (0-1 versus 2-3-4). The output of the final logistic regression model, including the prespecified variables, was exponentiated to obtain odds ratios (OR) and confidence intervals at 95%, calculated using the likelihood function. The statistical significance threshold was set at  $p < 0.05$ . All statistical analyses were performed with R Studio (RStudio Team, 2020).

## Ethic

Patients' records were anonymized prior to analysis. The database was constituted in accordance with the reference methodology MR004 of the *Commission Nationale de l'Informatique et des Libertés* (n°2206749, 13/09/2018), and followed the French authorities' requirements. A non-opposition form was given to each patient included in the study. The cohort CAPANCOVID-19 was registered on ClinicalTrials.gov (NCT04445870).

## Results

### Oncogenetic practices

The characteristics of the 833 patients included in the initial CAPANCOVID study have been previously published [21]. The median age at diagnosis was 70.0 years (IQR: 62.0 to 76.0 years) with a balanced sex ratio, 79.6% (n = 637) in a good medical condition and 45.7% of metastatic disease at diagnosis.

One hundred patients (12%) were declared eligible for referral to a GC by the local MTBM, including 59 who effectively performed the consultation, yielding a 59% conversion rate. The median time between MTBM and the first consultation with GC was 55 days (IQR: 14.5 to 112 days). The median time between the first consultation with GC and the delivery of the results to the patient was 91 days (IQR: 49 – 174 days).

### Implementation of French and international GC referral

A total of 460 patients were included in the 5 largest centres, accounting for 55.2% of the initial cohort (**Table 1**). The median age was 70 years old (IQR: 62.0 to 77.0) with a balanced sex ratio (women: n=244, 53.0%) and a good PS (0 or 1: n=357, 79.5%).

Twenty-eight patients were younger than 50 years old (6.1%). At diagnosis, approximately one quarter (n=105, 23.0%) of the patients had a resectable disease whereas 45.7% (n=209) had a metastatic disease. The characteristics of this subgroup were balanced compared to the overall initial cohort.

Among these 460 patients, 44 (9.6%) were referred for GC including 20 in priority (4.3%). A total of 95 (20.7%) and 170 (37%) had at least one history of cancer, personally or in the family, respectively. (**Table 2**).

A total of 305 patients were rightfully referred or not in an oncogenetic care pathway yielding a 66.3% adequacy rate (**Table 1**). Thirty-four patients were referred with a valid indication (7.4%). On the contrary, 145 (31.5%) patients with a significant personal or familial history were not referred for GC. The overall mismatch rate was 33.7% (n = 155). The most frequent mutation suspected was *BRCA*, with 121 patients (26.3%). Among those, 81.8% did not undergo the required GC (n=99/121) (**Table 3**). When performed, GC consultations were mainly indicated for a suspected *BRCA* (n = 22/44, 50%) or *PALB2* (n = 11/44, 25%) mutation carrying, FPC (n = 7/44, 15.9%), suspected Lynch syndrome (n = 5/44, 11.4%) and suspected *CDKN2A* (n = 2/44, 4.5 %) mutation carrying. (**Table 3**).

### **Factors associated with GC referral**

The factors associated with GC referral in the 5 largest centres are presented in **Table 4**. After adjusting on the prespecified covariates, older age (OR: 0.95 for each incremental year [CI95%: 0.91-0.98],  $p=0.002$ ) and locally advanced PA (OR: 0.17 [CI95%: 0.03-0.93],  $p=0.045$ ) were significantly associated with decreased odds of being referred for GC. On the contrary, being suspected of carrying a *CDKN2A* (OR: 16.63 [IC95%: 0.89-218.67],  $p=0.032$ ) or *BRCA* (OR: 118.46 [IC95%: 51.10-309.67]

$p < 0.001$ ) mutation using current guidelines, having a familial history of FPC (OR: 28.50 [IC95%: 8.50-104.01],  $p < 0.001$ ) and having a controlled disease during first-line platinum-based chemotherapy (OR: 169.44 [IC95%: 40.51-1189.92],  $p < 0.001$ ) were associated with greater odds of being referred to a GC. Suspected Lynch syndrome using guidelines did not remain significant in the adjusted analysis (OR: 2.17 [IC95%: 0.63-8.97],  $p = 0.246$ ) compared to the univariate analysis (OR: 10.50 [IC95%: 4.17-32.00],  $p < 0.001$ ). The additional sensitivity analyses confirmed the significance of the 50 years old threshold, whereas merged PS remained non-significant. The logistic regression models with a 50-year threshold or an aggregated PS did not perform better.

## Discussion

In this study, 12% of patients had an indication of GC referral, with 41% of missed consultation, and a median delay between MTBM and GC consultation of 55 days. In the subgroup of 460 patients with retrospectively collected personal and familial history, approximately one-third (31.5%) of the indicated GC referral were missed and 66.5% were rightfully referred or not to a GC. Patients suspected with a suspicion of *CDKN2A* or *BRCA* mutation using current guidelines, FPC history or achieving disease control with first-line platinum-based chemotherapy were significantly more referred for GC.

Twelve percent of patients in the overall cohort had an indication to be referred to a GC according to the local MTBM, with 41% missed in the end. Previous studies have tried to underline the discrepancies between real-world practices and adherence to guidelines, with heterogeneous findings [23–27]. Dudley *et al.* described a genetic

testing rate of 11.5% in an 11-year-long American monocentric cohort of PA [24]. Among those, only 42.3% respected the pre-2019 targeted National Comprehensive Cancer Network (NCCN) criteria, which could reflect an overtesting policy [24]. Moreover, 22.7% of the individuals who harboured a germline mutation did not meet the NCCN criteria [24]. Conversely, Catts *et al.* observed an overall referral rate of 52.7% for 332 PA in Delaware, USA, resulting in 47.3% missed indications [25]. However, we should underline the healthcare system and GC referral guidelines discrepancies preventing us from comparing these studies face-to-face. GC referral is the first step towards germline mutation identification. In France, germline testing is prescribed by GC in healthy individuals but can be delegated to trained oncologists for therapeutic purposes. In the USA, since 2019, the NCCN advises physicians to apply universal testing for patients diagnosed with PA due to discrepancies between relevant personal and familial histories and effective pathologic germline variant findings [28]. This dogma is opposed to what is currently implemented in European countries [29–32]. A noteworthy proportion of patients diagnosed with a mutation do not have a relevant familial history [33]. However, this universal testing attitude is still under debate [29–31]. However, to the best of our knowledge, no economic analysis of this approach has addressed the question. Further cost-effectiveness analyses are necessary to support this strategy. Promising leads also include a somatic *BRCA* before genetic testing.

The observed median delay between the MTBM decision and the GC consultation was 55 days in our study. Chittenden *et al.* found a similar result (42 days), but the genetic analysis and the delivery of the results seemed faster (13 days for Chittenden *et al.* versus 91 days in our cohort including waiting times for a dedicated feedback

GC session) [34]. In 2020, the French national cancer institute (INCa) reported a median time to obtain an oncogenetic consultation of 10 weeks for the index case and 8 weeks for the kindreds [22,35]. However, the growing demand tends to overflow GC and increases waiting times. Consequently, a dedicated network has been set up to enable urgent GC, which should be used for patients with potential therapeutic perspectives and/or shorter life expectancies [22,35].

In the CAPANCOGEN study, a total of 31.5% of the patients had a missed GC referral consultation despite a validated indication and 66.5% were rightfully referred or not to a GC (adequacy rate). Fulton *et al.* observed a 73.3% adequacy rate in a British monocentric cohort of 400 PA patients. However, these results were based on small sample size, as only 14 patients were referred to a GC with 10 respecting the EUROPAC criteria. The CAPANCOGEN study was the largest cohort to explore GC referral rates in a European country for a wide range of indications. In our study, the observed conversion rate seemed low regarding the possible implications in terms of missed opportunities for screening or therapeutic choices. Moreover, we should highlight the gap between the original cohort and the subset of 460 patients. One hundred GC referral indications were identified by the local MTBM among 833 patients, whereas we identified 179 potential indications in the subgroup of 460 patients. This difference depicts a low conversion rate from MTBM despite available data. Automated systematic procedures or systematic questionnaires about familial history can lead to better referral rates [34,36]. Besides, geographical disparities in terms of GC density cannot be ignored [35,37]. By retrospectively collecting detailed personal and familial histories of cancer from patient records, we emphasised the potential of available but unused data and the difficulty to identify the patients with

relevant familial history. The multiplicity of the guidelines calls for a unified international consensus on GC referral and testing. An automated tool powered by artificial intelligence may also help warn physicians when referral criteria are respected. Compared to the new American NCCN guidelines, European societies still recommend a targeted germline testing policy, as pre-2019 NCCN guidelines [38,39]. Moreover, targeted guidelines have shown good performance parameters to identify mutation carriers, with a robust sensitivity and specificity (86.4% and 71.2% respectively) that need to be interpreted with caution regarding the context of a potential missed early detection of cancer in kindreds [40]. The universal testing policy also has its limitations that need to be considered, such as difficulty to interpret the results, low actionability, and unknown cost-effectiveness in this indication.

Finally, we also explored factors associated with a GC referral to assess the implementation of guidelines. In our multivariate logistic regression analysis, we observed an obvious independent association of the suspicion of *BRCA/PALB2* and *CDKN2A* carrying, FPC history, and platinum-based first-line chemotherapy sensitivity with GC referral. However, the statistical association was not preserved between the univariate and multivariate analysis for the Lynch syndrome. It should be noted that this association was based on a small number of events and could be the result of an underpowered analysis. Also, older age and a locally advanced disease were less likely to be referred to GC. Germline mutation may be associated with younger age in physicians' general common sense, and a greater chance of early detection in the kindreds. However, younger age is not part of the GC referral indication on its own but appears as an influential factor in other related diseases [7,17–20,41]. This subjectivity in referral indications has already been emphasised by

Walker *et al.* [23]. Moreover, locally advanced diseases have never been shown to be associated with lower GC referral in previous studies. Despite the wide confidence interval and the low number of patients with locally advanced PA, we could hypothesize that this subset of patients, despite its advanced disease, are less prone to receive platinum-based chemotherapy as a first-line treatment and are not included in the official approval of olaparib [15]. Further data is needed to better explain the phenomenon.

This study had limitations. First, by choosing the referral rate as an endpoint, we deliberately focused on a necessary but insufficient step to identify a genetic mutation. Indeed, patients could refuse genetic testing or could be explored during a previous personal or familial cancer diagnosis. Moreover, PA has a poor prognosis with sometimes fast general condition alterations or death that could precede genetic testing. Secondly, we did not collect genetic mutation results to measure the testing performances of these guidelines. These results have already been published in previous large studies [40]. Thirdly, the risk of Ashkenazi Jews could not be individualised as the collection of ethnic, racial, or religious data is not permitted in France. Additionally, the age of familial cancer diagnosis was not collected. This could have brought more information regarding the probability of germline mutation and refined the conclusions. Finally, the CAPANCOVID cohort was mainly constituted of tertiary care centres blinding a non-negligible source of GC referral. Even if it encompassed the pandemic period, the CAPANCOVID cohort found no influence of the pandemic on the number of new diagnoses. Also, it should be noted that the French National Institute for Cancer observed a decrease in the number of first consultations by 5%, which remains limited [22,35].

## **Conclusion**

Despite significant personal or family histories already collected and available in the medical files, approximately one-third of patients diagnosed with a PA were not referred for GC, potentially decreasing their chances of receiving a targeted treatment or early diagnosing their relatives. A new pathway from the physician to the GC should be considered to avoid any missed opportunities. Better disseminated unified international guidelines and tools could lead to enhance adequacy rates.

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## **Author Contributions**

**Mathias Brugel:** Conceptualization, Methodology, Formal analysis, Project administration, Validation, Visualization, Writing - original draft, Writing- review & editing, Funding acquisition. **Thibault Marulier:** Conceptualization, Investigation, Writing - original draft, Writing- review & editing. **Claire Carlier:** Conceptualization, Investigation, Validation, Writing- review & editing. **Marine Perrier:** Conceptualization, Investigation, Validation, Writing- review & editing. **Olivier**

**Bouché:** Conceptualization, Investigation, Project administration, Resources, Supervision, Writing - original draft, Writing- review & editing, Funding acquisition. **All other authors:** Investigation, Resources, Writing- review & editing.

### **Conflict of Interest Statement**

C.C. reports personal fees as a speaker from Bristol Myers Squibb, outside the submitted work. D.T. reports personal fees as a speaker and/or in an advisory role from Merck KGaA, Roche, Bayer, Astra-Zeneca, BMS, MSD, Amgen, Sanofi, Servier, Ipsen and Pierre Fabre, outside the submitted work. G.P. reports personal fees as a speaker and/or in an advisory role from BMS, MSD, Stryker and Medtronic, outside the submitted work. A.T. reports personal fees as a speaker and/or in an advisory role from Merck KGaA, BMS, MSD, Servier, Mylan and Pierre Fabre and travel accommodations expenses from AstraZeneca, outside the submitted work. D.B. reports personal fees as a speaker and/or in an advisory role from Accord Healthcare, Amgen, Sanofi, Servier, and Pierre Fabre, outside the submitted work. O.B. reports personal fees as a speaker and/or in an advisory role from Apmomia Therapeutics, Merck KGaA, Bayer, Grunenthal, MSD, Amgen, Servier, and Pierre Fabre, outside the submitted work.

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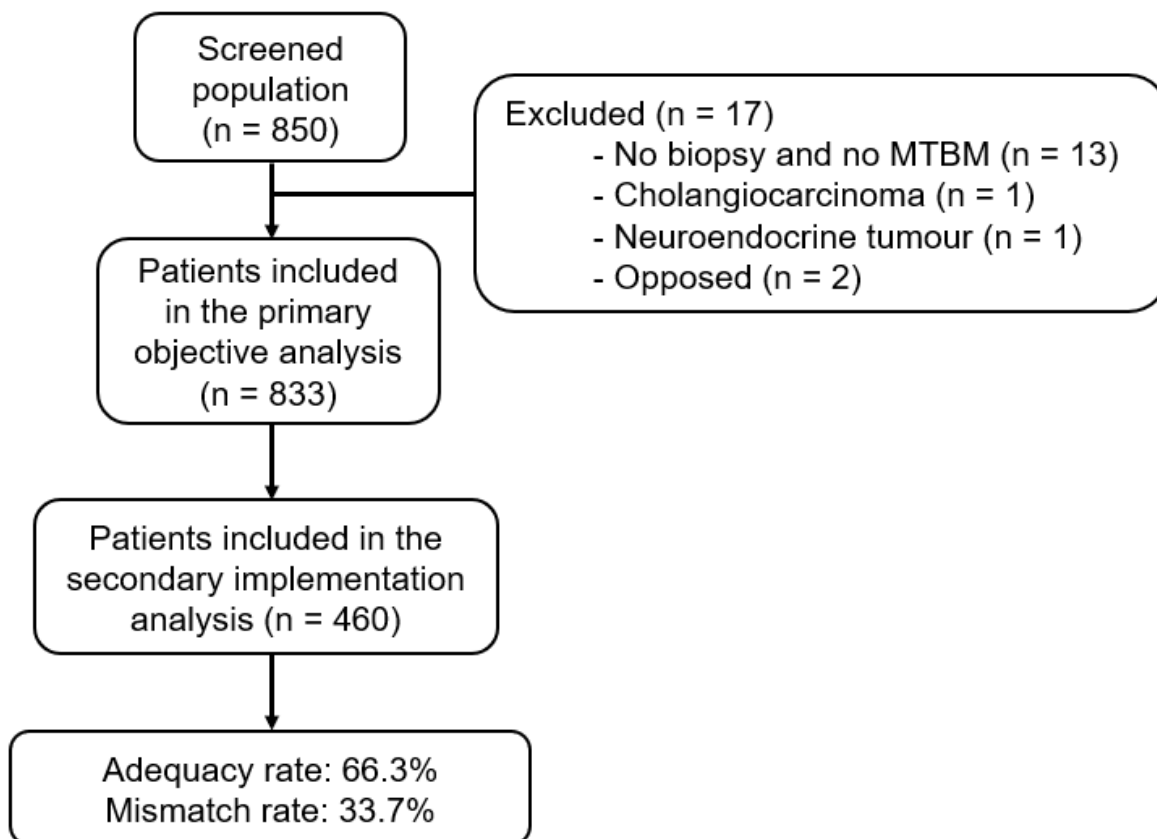
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**Figure 1. Flow chart diagram**

n=number of patients; MTBM: Multidisciplinary Tumour Board Meeting; GC: genetic counselling

**Table 1. Baseline characteristics and oncogenetic care pathway in the 5 largest centres (n=460)**

<b>Variables</b>	<b>Levels</b>	<b>Overall (n=460)</b>
Gender (%)	Women	244 (53.0)
Age (years)	Median (IQR)	70.0 (62.0 to 77.0)
Including centre (%)	Reims University Hospital	160 (34.8)
	Reims Cancer Institute	20 (4.3)
	Saint Etienne University Hospital	61 (13.3)
	Poitiers University Hospital	114 (24.8)
	Lille University Hospital	105 (22.8)
Distance between home and care centre (km)	Median (IQR)	35.0 (10.0 to 71.0)
Performance status (%)	0	141 (31.4)
	1	216 (48.1)
	2	60 (13.4)
	3	24 (5.3)
	4	8 (1.8)
	Missing	11 (2.4)
BMI (kg/m <sup>2</sup> )	Median (IQR)	24.2 (21.4 to 27.6)
Tumour location (%)	Head	290 (63.5)
	Body	90 (19.7)
	Tail	77 (16.8)
	Missing	3 (0.7)
Histopathological confirmation (%)	Yes	421 (91.5)
Plasma CA19-9 (UI/L)	Median (IQR)	373.0 (53.2 to 2008.0)
Disease stage (%)	Resectable	105 (23.0)
	Borderline	65 (14.2)
	Locally advanced	78 (17.1)
	Metastatic	209 (45.7)
Genetic counselling referral indication according to local MTBM (%)	Yes	61 (13.3)
Genetic counselling consultation performed (%)	Yes	44 (9.6)
Priority genetic counselling consultation (%)	Yes	20 (45.5)
First-line therapeutic strategy (%)	Surgery	62 (13.5)
	Induction chemotherapy	115 (25.0)
	Palliative chemotherapy	230 (50.0)

	Best supportive care	53 (11.5)
Implementation quality measurement (%)		
Indicated (%)		179 (38.9)
Not indicated (%)		281 (61.1)
Performed (%)		44 (9.6)
Not performed (%)		416 (90.4)
Indicated but not performed		145 (31.5)
Indicated and performed		34 (7.4)
Not indicated and not performed		271 (58.9)
Not indicated but performed		10 (2.2)
Adequacy rate (%)		305 (66.3)
Mismatch rate (%)		155 (33.7)

n: number of patients; IQR: Interquartile range; BMI: body mass index; km: kilometre;

kg/m<sup>2</sup>: kilogram per square metre; UI/L: international unit per litre

**Table 2. Personal and familial history of cancer, by tumour site and degree in the 5 largest centres (n=460)**

	Personal	1 <sup>st</sup> degree	2 <sup>nd</sup> degree	≥ 3 <sup>rd</sup> degree	Missing
<b>Total number of patients with a personal or familial history of cancer (%)</b>	95 (20.7)	170 (37.0)			6 (1.3)
<b>Total number of personal or familial tumours</b>	103	164	59	22	9
Number of personal or familial pancreatic cancer (%)	0 (0)	20 (12.2)	8 (13.6)	3 (13.6)	0 (0)
Number of personal or familial breast cancer (%)	23 (22.3)	24 (14.6)	16 (27.1)	9 (40.1)	2 (0.6)
Number of personal or familial ovarian cancer (%)	3 (2.9)	5 (3)	3 (5.1)	2 (9)	0 (0)
Number of personal or familial endometrial cancer (%)	4 (3.9)	8 (4.9)	0 (0)	1 (4.5)	0 (0)
Number of personal or familial colorectal cancer (%)	9 (8.7)	24 (14.6)	6 (10.2)	1 (4.5)	0 (0)
Number of personal or familial stomach cancer (%)	0 (0)	3 (1.8)	2 (3.4)	0 (0)	0 (0)
Number of personal or familial small intestine cancer (%)	0 (0)	0 (0)	1 (1.7)	0 (0)	0 (0)
Number of personal or familial bile duct cancer (%)	1 (1.0)	3 (1.8)	2 (3.4)	0 (0)	0 (0)
Number of personal or familial prostate cancer (%)	16 (15.5)	9 (5.5)	1 (1.7)	2 (9)	2 (0.6)
Number of personal or familial urinary tract cancer (%)	6 (5.8)	8 (4.8)	1 (1.7)	0 (0)	0 (0)
Number of personal or familial melanoma (%)	7 (6.8)	5 (3)	1 (17)	0 (0)	0 (0)
Number of personal or familial other tumours (%)	34 (33)*	55 (33.5)	18 (30.5)	4 (18.2)	5 (1.4)

\* Other personal histories of cancer include, among others, 13 hemopathies, 4 lung cancers, 4 thyroid cancers, and 3 kidney cancers.

A patient can have a history of several personal or familial tumours.

**Table 3. Indications of genetic counselling referral according to the status of the consultation (not performed versus performed) (N=460).**

Variables	Not performed (n=416)*	Performed (n=44)*	Total per strata*
CAPS A1	0 (0)	0 (0)	0
CAPS A2	0 (0)	0 (0)	0
CAPS A3	13 (65)	7 (35)	20
CAPS A4	0 (0)	0 (0)	0
CAPS A5	0 (0)	0 (0)	0
CAPS A6	3 (60)	2 (40)	5
CAPS A7	0 (0)	0 (0)	0
CAPS A8	1 (50)	1 (50)	2
CAPS A9	0 (0)	1 (100)	1
Suspicion of carrying a <i>CDKN2A</i> mutation	3 (60)	2 (40)	5
Suspicion of carrying a <i>BRCA</i> mutation	99 (81.8)	22 (18.2)	121
Suspicion of carrying a <i>PALB2</i> mutation	20 (64.5)	11 (35.5)	31
Suspicion of Lynch syndrome	21 (80.8)	5 (19.2)	26
Familial pancreatic cancer	14 (66.7)	7 (33.3)	21
Sensitivity to platinum-based first-line chemotherapy for metastatic PA	22 (91.7)	2 (8.3)	24
Age < 50 years old	19 (67.9)	9 (32.1)	28

CAPS: International of the Pancreas Screening Consortium [17,18]; PA: pancreatic adenocarcinoma; *BRCA 2*: Breast cancer 2; *PALB2*: Partner and localizer of *BRCA2*; *CDKN2A*: cyclin-dependent kinase inhibitor 2A; n: number of people

\* One patient could have several suspicions. Therefore, the total is not equal to the number of patients.

**Table 4. Univariate and multivariate logistic regression of associated baseline characteristics according to the GC referral status.**

Variables	Levels	Patients referred to GC(n=315) (%)	Patients not referred despite having an indication (n=145) (%)	Univariate OR (CI95%, p-value)	Multivariate OR (CI95%, p-value)
Age (years)	Median (IQR)	70 (62.0 to 77.0)	70 (62.0 to 77.0)	0.99 (0.97-1.01, p=0.180)	0.95 (0.91-0.98, p=0.002)
Gender	Men	151 (69.9)	65 (30.1)	Ref.	Ref.
	Women	164 (67.2)	80 (32.8)	1.13 (0.76-1.68, p=0.535)	1.29 (0.64-2.62, p=0.476)
Performance status	0	98 (69.5)	43 (30.5)	Ref.	Ref.
	1	143 (66.2)	73 (33.8)	1.16 (0.74-1.84, p=0.515)	0.96 (0.43-2.13, p=0.918)
	2	43 (71.7)	17 (28.3)	0.90 (0.45-1.74, p=0.759)	1.44 (0.40-5.07, p=0.573)
	3	20 (83.3)	4 (16.7)	0.46 (0.13-1.29, p=0.174)	1.08 (0.08-11.11, p=0.949)
	4	5 (62.5)	3 (37.5)	1.37 (0.27-5.83, p=0.678)	3.46 (0.17-71.87, p=0.431)
Disease stage	Resectable	67 (63.8)	38 (36.2)	Ref.	Ref.
	Borderline	51 (78.5)	14 (21.5)	0.48 (0.23-0.97, p=0.046)	0.88 (0.20-3.90, p=0.864)
	Locally advanced	58 (74.4)	20 (25.6)	0.61 (0.31-1.15, p=0.131)	0.17 (0.03-0.93, p=0.045)
	Metastatic	138 (66.0)	71 (34.0)	0.91 (0.56-1.49, p=0.697)	0.43 (0.08-2.29, p=0.324)
First-line therapeutic strategy	Surgery	36 (58.1)	26 (41.9)	Ref.	Ref.
	Induction chemotherapy	90 (78.3)	25 (21.7)	0.38 (0.20-0.75, p=0.005)	0.27 (0.06-1.21, p=0.091)
	Palliative chemotherapy	149 (64.8)	81 (35.2)	0.75 (0.43-1.34, p=0.331)	1.15 (0.18-7.42, p=0.885)
	Best supportive care	40 (75.5)	13 (24.5)	0.45 (0.20-0.99, p=0.052)	1.67 (0.15-15.16, p=0.661)
Distance between home	Median (IQR)	38.0 (11.0 to 70.0)	27.5 (10.0 to 78.0)	1.00 (1.00-1.00, p=0.617)	1.00 (0.99-1.00, p=0.457)

Variables	Levels	Patients referred to GC(n=315) (%)	Patients not referred despite having an indication (n=145) (%)	Univariate OR (CI95%, p-value)	Multivariate OR (CI95%, p-value)
and care centre (km)					
Suspicion of <i>CDKN2A</i> according to the criteria	Absent	313 (68.8)	142 (31.2)	Ref.	Ref.
	Present	2 (40.0)	3 (60.0)	3.31 (0.54-25.31, p=0.193)	16.63 (0.89-218.67, p=0.032)
Suspicion of <i>BRCA</i> according to the criteria	Absent	293 (86.4)	46 (13.6)	Ref.	Ref.
	Present	22 (18.2)	99 (81.8)	28.66 (16.72-51.08, p<0.001)	118.46 (51.10-309.67, p<0.001)
Suspicion of Lynch syndrome according to the criteria	Absent	310 (71.4)	124 (28.6)	Ref.	Ref.
	Present	5 (19.2)	21 (80.8)	10.50 (4.17-32.00, p<0.001)	2.17 (0.63-8.97, p=0.246)
Sensitivity to first-line platinum-based chemotherapy for 16 weeks for metastatic PA	Absent	313 (71.8)	123 (28.2)	Ref.	Ref.
	Present	2 (8.3)	22 (91.7)	27.99 (8.09-176.38, p<0.001)	169.44 (40.51-1189.92, p<0.001)
Familial pancreatic cancer according to the criteria	Absent	308 (70.2)	131 (29.8)	Ref.	Ref.
	Present	7 (33.3)	14 (66.7)	4.70 (1.91-12.66, p=0.001)	28.50 (8.50-104.01, p<0.001)

GC: genetic counselling; OR: odds ratio; CI95%: confidence interval 95%; IQR:

Interquartile range; Ref.: stratum of reference; PA: pancreatic adenocarcinoma;