Bando 2019 - Programma 5 per mille anno 2019 Investigator Grant (IG)

TRANSLATIONAL RESEARCH

1.Principal investigator's full name and qualification:

Paola Ghiorzo (PI)
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(CV in European format with list of publications; IF end Hi-index attached)

2. Proposal title: **Beyond *BRCA*: hereditary cancer predisposition and personalized therapy by multigene panel testing in pancreatic cancer patients**
3. Primary area of Relevance: Cancer Genetics
4. Relevance for the National Health System: The results of this study will have valuable clinical and research implications in the short and medium term. First, offering germline susceptibility testing to all consecutively enrolled pancreatic cancer (PC) patients will help broaden the population eligible to targeted therapy, such as PARP inhibitors in *BRCA* mutated patients, thus increasing therapeutic options for these patients. Second, identifying the subset of PC patients who bear germline pathogenic variants associated with specific hereditary syndromes, and their non-affected high-risk relatives, will allow referring them to genetic counseling and offering them enrolment in surveillance programs. Third, involving oncologists in this process will increase their awareness of hereditary PC syndromes and of the potential therapeutic implications of germline genetic findings in PC patients.
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9. Place and date: Genoa, 17.02.2020

2 SELF EVALUATION FORM
1. Investigator's full name: (PI) Paola Ghiorzo
2. Total papers: 108 (IF 846)
3. Total papers (last 10 years): 79 (IF 582)
4. Total Papers as first/last author or corresponding author: 31
5. Total H-index: 36

PROPOSAL MAIN BODY

1. Proposal title: Beyond *BRCA*: hereditary cancer predisposition and personalized therapy by multigene panel testing in pancreatic cancer patients

2. ABSTRACT

Rationale

Widespread availability of next generation sequencing technologies (NGS), which has resulted in increased detection of Pathogenic Variants (PVs) and Variants of Unknown Significance (VUS) through multigene panel testing, has led to a paradigm shift in cancer susceptibility testing. While previously no more than 10% of Pancreatic Cancer (PC) cases were considered due to heritable factors, only a subset of which was explained by germline PVs in high risk genes, recent sequencing efforts have found that as many as 15% of PC patients unselected for family history bear PVs. In addition, recent results from the POLO trial showed the efficacy of anti-PARP molecules in germline *BRCA* positive patients. Therefore, international guidelines recommend multigene germline testing for all PC patients. However, translating these guidelines into clinical practice may be challenging, as the clinical utility of panel testing in PC patients remains to be clearly understood, especially for genes other than *BRCA1/2*. Therefore, we intend to conduct an observational study of oncologist-led Multiple Gene Panel (MGP) testing in all PC patients in order to select those patients carrying potentially druggable pathogenic variants in genes other than *BRCA1/2 or DNA mismatch repair* (MMR) genes. Patients who test positive to germline testing, together with relatives at high-risk for PC and other cancers, will be referred to genetic counseling and to specific surveillance programs when appropriate.

Preliminary results

At our center we have been conducting an ongoing observational study stemming mainly from our first characterization in Italy of the *CDKN2A* pancreatic-melanoma syndrome. Indeed, a multidisciplinary team (Geneticists, Oncologists, Bioethicists, Molecular Biologists, Pathologists and Epidemiologists) is already in place and we observed good compliance of patients to the mainstreaming approach. We have collected a retrospective consecutive series of 400 germline DNAs from PC patients unselected for family history. Among these, we found that , 4.5% harbored a pathogenic variant in the *CDKN2A* gene. The rate of *CDKN2A* PVs increased to 20 and 40% when patients affected by familial PC or the melanoma-PC syndrome, respectively, were considered separately. Moreover, we conducted whole exome sequencing in a subset of 54 high-risk patients and found that 13% harbored a pathogenic or likely pathogenic ATM variant. Finally, we tested the *BRCA1/2* and MMR genes in a subset of patients selected for having a suggestive family history, and found that 25% of these patients harbored a PV in one of these genes.

Detailed description of the translational value

The detection rate of PV and VUS identified using MGP testing varies among studies, depending on the panel used, patient selection and variant classification, and needs further validation in independent cohorts. In Italy, this estimate is missing. Furthermore, data on the somatic mutation rate in established and candidate PC predisposition genes are lacking due to technical limitations, scarce cellularity and difficulties in recruiting surgical specimens. Therefore, current recommendations for *BRCA* testing and treatment decisions are based on germline DNA testing, whereas somatic *BRCA1/2* testing and germline/somatic testing of other genes is limited to research protocols.

With this study, we expect to find a relevant rate of patients who harbor actionable variants, including *BRCA1/2*, and variants in other Homologous Recombination DNA Damage Repair (HR-DDR) genes, like *ATM*, which are of particular interest because of reported clinical trials enrolling these patients. Overall, the combination of germline testing with tumor mutational assessment will help discern the clinical relevance of PV variants and VUS in candidate genes and guide future therapeutic decisions, towards individualized patient care.

Expected impact on the NHS
The results of this study will have valuable clinical and research implications in the short and medium term. First, offering germline susceptibility testing to all consecutively enrolled PC patients will help broaden the population eligible for targeted therapy, such as PARP inhibitors in *BRCA* mutated patients, thus increasing therapeutic options for these patients. Second, identifying the subset of PC patients who bear germline pathogenic variants associated with specific hereditary syndromes, and their non-affected high-risk relatives, will allow referring them to genetic counseling and offering them enrolment in surveillance programs in research settings. Third, involving oncologists in this process will increase their awareness of hereditary PC syndromes and of the potential therapeutic implications of germline genetic findings in PC patients.

3. Introduction

Pancreatic ductal adenocarcinoma is one of the deadliest solid tumors, with an average 5-year survival rate of 5-7%. In 2018, 458,918 new cases and 432,242 deaths were observed globally (4.5% of all deaths caused by cancer) [1, 2], and this incidence is expected to increase [3]. Surgical resection is the only potential cure but, to date, it is possible in less than 20% of patients at the time of diagnosis [4].
Up to 10% of PC patients have a familial inheritance [5]: about 3% of PC derive from hereditary cancer syndromes, and another 7% are classified as Familial PC (FPC), which is defined as an individual who has two or more first-degree relatives with PC [6]. However, there are no established screening procedures either for high-risk unaffected cases or for the general population, and it is not clear whether surveillance programs would have clinical benefits [6].
Hereditary PC syndromes include: HBOC, Peutz-Jeghers syndrome, Familial Atypical Multiple Mole Melanoma (FAMMM)/melanoma-pancreatic cancer syndrome, Lynch syndrome (or Hereditary NonPolyposis Colorectal Carcinoma [HNPCC]), Familial Adenomatous Polyposis (FAP), ataxia-telangiectasia (ATM), and Hereditary Pancreatitis (HP). These hereditary cancer syndromes account for 10-15% of hereditary PC, while the genetic etiology of the majority of FPC has yet to be identified [7-9].

In 2010, the Italian Association for the Study of the Pancreas (AISP) developed a position paper for the surveillance of subjects at high-risk of PC, including high-risk individuals with familial and/or genetic predisposition [10], and in 2015 an official registry of asymptomatic high-risk individuals was created following these guidelines. Recently, Paiella and colleagues reported the results of the first-round of screening [11]. These data emphasize the increasing interest of the scientific community in developing a cost-effective standardized surveillance program for individuals at high-risk of PC. However, larger studies are still warranted to assess the benefits of surveillance in high-risk individuals in term of reduction of mortality.

Despite the lack of an internationally validated surveillance program for high-risk individuals, the National Comprehensive Cancer Network (NCCN) 2019 guidelines already recommend multigene germline testing for any patient with a confirmed PC diagnosis[12].

However, the implementation of this recommendation is hampered by the uncertainty around the clinical utility of multigene testing in PC patients, particularly for genes other than *BRCA1/2*. Indeed, (MGP testing result in a high rate of PVs, whose spectrum of cancer risk, as well as penetrance is often not clearly defined. In addition, MGP testing generates high rates of VUS. These issues are of concern in the medical community, as ambiguous findings may lead to unnecessary patient anxiety and unwarranted interventions [13].

The recent results of the POLO trial [14] confirmed the proof of principle of anti-PARP (Poly ADP-ribose polymerase) efficacy in germline *BRCA* positive PC patients. In addition to ovarian and breast cancer patients, the efficacy shown in this study extended the population of patients to be tested and counseled for *BRCA* pathogenic variants (PV) to PC patients. In addition, some of the other above-mentioned hereditary syndromes associated with PC (i.e., Lynch Syndrome) are known to be caused by actionable mutations [15]. Oncologists tend to be focused on treatment and to overlook the implications of genetic counseling and diagnosis of hereditary syndromes, mainly for relatives' involvement. Thus, the POLO trial's results have two main implications: a) the need to select *BRCA* germline positive patients for personalized therapy; b) the need to adequately counsel them for hereditary cancer syndromes.

We are witnessing to a radical shift in the standard of care of genetic counseling process [16]: rather than submitting patients to pre- and post-genetic testing session, we are called to perform mainstream, oncologist-led, family history independent genetic testing and refer for counseling only those who are found to be positive [17], as advocated by NCCN for PC [12].
In addition, widespread availability of next generation sequencing technologies (NGS), which has resulted in increased detection rates of PVs and VUS through multigene panel testing, has led to a paradigm shift in cancer susceptibility testing. While previously no more than 10% of Pancreatic Cancer (PC) cases were considered due to heritable factors, only a subset of which was explained by germline PVs in high risk genes, recent sequencing efforts have found that as many as 15% of PC patients unselected for family history bear PVs.
Among the genes tested and frequently found positive are: *ATM, CHEK2, NBN* and other Homologous Recombination DNA Damage Repair (HR-DDR) genes, *CDKN2A, PALB2* and DNA Mismatch Repair (MMR) genes. The highest detection rate (19,8%) was found by Lowery et al in PC patients unselected for family history, and between 5-10% of PV were judged therapeutically actionable [18]. This figure, however, varies among studies, depending on panel used, patient selection, and variant classification, and needs further confirmation in independent cohorts.
There are ongoing clinical trials carried out on PC patients harboring PVs including *ATM* and other DNA damage repair genes as well as *BRCA1/2*. Most of these studies are not PC-specific, but explore the potential benefits on novel target therapies in multiple solid cancers [19].

4. Background and rationale

Following the POLO trial, during 2019, in a joint effort among the Italian scientific societies of oncologists, human geneticists, pathologists, and clinical biochemistry (AIOM, SIGU, SIAPEC and SIBIOC), we developed recommendations for prospectively testing for germline *BRCA1* and *BRCA2*, in the framework of the National Health System, all metastatic PC patients, in order to select carriers of PVs eligible for treatment with PARP inhibitors [20].
Therefore, several centers in Italy, including ours, are recruiting in a diagnostic setting DNA samples from PC patients for *BRCA1* and *BRCA2* genetic testing to direct therapy.
The overall detection rate is estimated to be around 2-4% but this rate varies among studies, and it needs to be confirmed prospectively, and, in the short term, retrospectively in specific unselected population. These data are still not available in Italy. In addition, data on the somatic mutation rate in these genes are lacking due to technical limitations, scarce cellularity and difficulties in recruiting surgical specimens. Therefore, current recommendations for *BRCA* testing and treatment decisions are based on germline DNA testing, with somatic testing of BRCA1/2 and germline/somatic testing of other genes being still limited to research protocols.

In our center, an observational study is ongoing stemming mainly from our first characterization in Italy of the *CDKN2A* pancreas-melanoma syndrome, and we have a retrospective consecutive

collection of 400 germline DNAs from PC patients not selected based on family history . Therefore, a multidisciplinary team (Geneticists, Oncologists, Bioethicists, Molecular Biologists, Pathologists and Epidemiologists) is already in place, and we observed a good compliance of patients to the mainstreaming approach, with almost all patients accepting an oncologist-driven blood sample withdrawn for genetic testing, followed by genetic counseling of positive patients. Patients signed their consent for research as well as for tissue studies. For a subset of patients in this dataset (around 40%) PC tissue is available. Similarly, prospective genetic testing for *BRCA1* and *2* has already begun, and a subset of DNA samples is already available.

Due to these reasons, we propose an observational study of an oncologist-led multiple-gene panel testing in all PC patients in order to select those patients carrying potentially druggable PVs other than in *BRCA or mismatch repair* (MMR) genes. For example, PVs in *ATM* and other HR-DDR genes could be targeted by PARP inhibitors. We aim to define germline, and possibly somatic mutation rates in these genes, by testing all DNA samples with the same panel regardless of family history. Tissue gene expression analysis and LOH of candidate germline variants in these genes will help define the pathogenicity of variants with unknown significance (VUS).
In addition, patients who test positive to germline testing will be referred to genetic counseling and to specific research surveillance program when appropriate [11], together with their relatives at high-risk for PC (Figure 1).

5. Experimental design (organized in tasks)

Aims and endpoints of the study
We aim to demonstrate the feasibility of an extended, streamlined, oncologist-led, MGP germline testing in all PC patients followed by genetic counseling for those patients found to carry a germline PV. Our main secondary aim will be to determine the correlation between somatic and germline PVs in this latter subset.
Primary aims:
- To optimize the mainstreaming diagnostic algorithm and evaluate its feasibility, in order a) to assess the prevalence of druggable PVs and b) to select patients for specific genetic counseling.
- To increase oncologists' awareness of the importance of hereditary syndromes diagnosing and their adherence to international guidelines.
-To identify potentially druggable PVs in PC susceptibility genes, other than *BRCA1/2*, prospectively and retrospectively. Specifically, we will focus on *ATM* and HR-DDR related PVs to confirm preliminary data and to select patients candidate for enrolment in clinical trials.
-Test the patients' tumors to confirm LOH, and clarify pathogenicity, and/or feasibility of tumor testing for candidate variants selected from germline analysis.
Secondary aims:
- To increase the frequency of hereditary syndrome diagnosis and the number of at-risk relatives of patients to be enrolled in targeted screening and prevention programs.
- To evaluate the correlation between somatic and germline variations.
- To reduce pressure on specialist genetics services.
- Number of patients who test positive in one of the genes included in the panel and could be directed to clinical trials

Endpoints
- Compliance of Oncologists and patients to the protocol (percentage of patients screened, enrolled, tested, referred to genetic counseling; rate of patients' acceptance to the study)
- Percentage of patients diagnosed with a hereditary syndrome.
- Percentage of relatives carriers of the selected germline variant.
- Percentage of patients and high-risk relatives enrolled in specific research surveillance program.

- Comparison between somatic and germline mutations rate.

To achieve these aims, the project will be organized in the following tasks, limited to the first year of activity.

Task1
Design, validation and MGP testing. Experienced researchers from the group (see group composition) will design and validate a custom designed panel containing *BRCA1/2, ATM, PALB2, CDKN2A, MLH1, MSH2/6, PMS2, EPCAM, APC, STK11, PRSS1, SPINK1, BARD1, NBN, CDK12, FANCC, NTRK, MRN, MRE11, RAD50/51/C/D, ARID1A/B/2, ATR, ATRX, CHECK1/2.* Positive controls are already available for validation. *BRCA* results will be compared with those from the diagnostic setting.
Task 2
MGP testing in a retrospective (100) and a prospective cohort (60 per year estimated). Annotation, variant classification and calculation of detection yield % (PVs and VUS) in candidate genes will be performed.
Task 3
Somatic PC tumor testing from patients carriers of germline PV or VUS to evaluate somatic status of candidate genes, assess LOH when appropriate and gene expression by Immunohistochemistry (IHC). This analysis will be of help in determining the real effect of the germline variant in the cancer tissue and help contribute to functional assessment of VUS.
Task 4
Carriers of actionable PV, determining a high risk of developing PC will be directed to genetic counselling and testing of family members in order to discuss specific research surveillance protocols.
Task 5
Overall compliance of oncologists and patients to the protocol will be evaluated. The % of patients carriers of druggable PVs in PC susceptibility genes, other than *BRCA1/2*, will be evaluated prospectively and retrospectively.

6. Further details on the overall methods that will be used in this project

All DNA samples are already available from patients selected for either research o clinical genetic testing as described above. All consecutive PC patients referred to the Oncology Units at IRCCS Ospedale Policlinico San Martino (Genova, Italy) included in this study will undergo the following diagnostic algorithm:
- Oncologist-led consent and blood-taking for genetic testing. Proposed MGP: *BRCA1/2, ATM, PALB2, CDKN2A, MLH1, MSH2/6, PMS2, EPCAM, APC, STK11, PRSS1, SPINK1, BARD1, NBN, CDK12, FANCC, NTRK, MRN, MRE11, RAD50/51/C/D, ARID1A/B/2, ATR, ATRX, CHECK1/2.*
- In case of a positive test, the laboratory Geneticist will communicate the result to the Oncologist, who will refer the patient for post-test Genetic Counseling.
- Family history will be evaluated through an "ad hoc" validated questionnaire administered to all patients to select individuals with non-informative genetic testing but with FPC. FPC is defined if having: ≥ 3 relatives affected by PC until the third degree of kinship or 2 relatives affected if at least one being a first-degree relative.
- A satisfaction questionnaire for patients and health professionals involved in the novel mainstreaming approach will be developed and administered at the end of the diagnostic process.
- Surveillance research protocols will be shared with other centers in Italy, in order to offer to individuals at risk-high quality programs in referral centers.
Quantity and purity of the genomic DNA (gDNA) will be examined by SPECTROstar Nano (BMG Labtech, Offenburg, Germany) to measure the whole absorption spectrum (220–750 nm) and

calculating absorbance ratios at both 260/280 and 260/230. Moreover, all samples will be quantified by Qubit® 2.0 Fluorometer (Invitrogen, Carlsbad, CA, USA). A custom panel targeting the 31 genes is designed using the Ion AmpliSeq Designer tool using the standard DNA (375 bp amplicon target sizes) option. Two primer pools are designed to amplify 813 amplicons, for a total length 233.72 kb. The NGS library will be constructed using the Ion AmpliSeq Kit for Chef DL8 (Thermo Fisher Scientific), according to the manufacturer's protocol starting from 20 ng of gDNA. Cycling conditions will be performed according to the DNA type and primer pairs per pool: 17 cycles with an extension time of 4 minutes in the first multiplex PCR, whereas in the second, optional PCR, the gDNA will be subjected to five cycles. The library concentration will be evaluated with a Qubit® 2.0 Fluorometer using the Agilent High Sensitivity DNA Kit (Life Technologies). After quantification, each library will be diluted to a concentration of 100 pM prior to template preparation. Subsequently, the libraries will be pooled in equimolar amounts prior to further processing. Emulsion PCR, emulsion breaking, and enrichment for template preparation of ion sphere particles will be performed using the Ion 510 & 520 & 530 Kit-Chef (Thermo Fisher Scientific) according to the instruction of the manufacturer. Sequencing will be performed with an Ion Torrent S5 GeneStudio Plus system using 530 Chip (Thermo Fisher Scientific), according to the instruction of the manufacturer. The S5 sequencing data were analyzed by the Ion Torrent Software Suite (ThermoFisher Scientific) using the plugin Variant Caller and IonReporter (ThermoFisher Scientific).
A combined analysis performing tissue IHC with specific antibodies directed to the actionable genes found to be mutated in the germline, and LOH performing sequencing DNA from the PC tissue to verify loss of expression and/or the second allele inactivation will be performed to help clarify pathogenicity of the germline variants of interest in candidate/actionable genes.

7. Work carried out and preliminary results

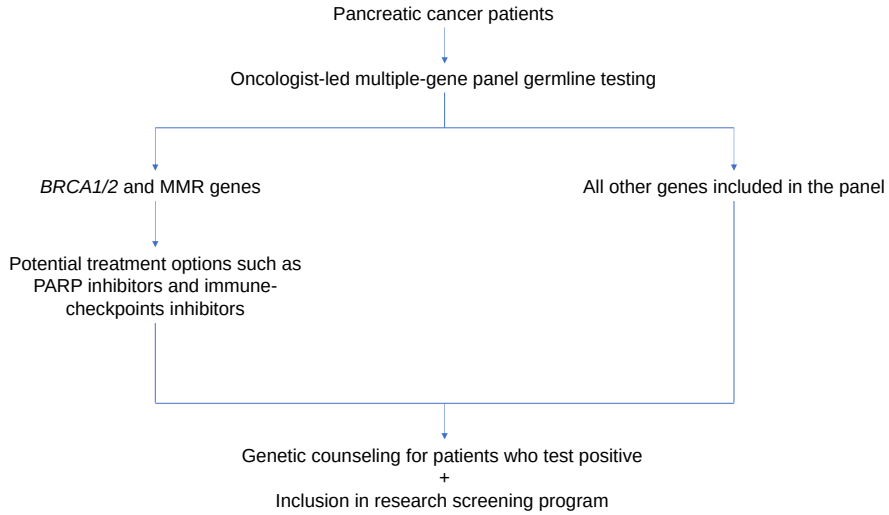
The retrospective cohort includes 400 patients diagnosed with PC, consecutively enrolled and unselected for family history. 4,5% of these patients harbored a pathogenic variant in the *CDKN2A* gene, whose germline mutational status was assessed in the whole cohort ([21] and unpublished data). *CDKN2A* pathogenic variants yield in our cohort is high and raises up to 20 and 40% in patients with FPC or melanoma-PC syndrome, respectively. Moreover, a subset of 54 patients (classified as high risk based on their family history) underwent whole exome sequencing, and 13% of these had a pathogenic or likely pathogenic *ATM* variant [22]. Information on *BRCA1/2* germline status is available for 30 patients, selected for a family history suggestive of HBOC syndrome, 25% of whom harbored a PV in either gene [23]. A similar detection rate in MMR genes was found for a subset of patients selected for a family history suggestive of Lynch syndrome [24]. For all patients, stored DNA samples from peripheral blood will be used to assess germline mutational status of the above-listed genes, if not available from previous DNA sequencing analysis.
A preliminary analysis of the retrospective cohort showed, out of the most recent 100 cases, FFPE tissue available in 36 patients (18 samples from surgery and 18 from punch biopsies).
A collaboration with the pathologists is already in place and proved to be effective in molecular testing, also by NGS, of tumors from our pathology Department. We expect to collect a higher number of tumor specimens in the prospective series.

8. Expected results and relevant corresponding milestones

Milestone1. During the year one of the project we will be able to test and validate, by the designed gene panels, 100 retrospective cases and all the consecutive cases recruited during one year (N=60). Based on the literature and on preliminary data, we realistically expect to find a low (below 10%), but relevant % of patients carriers of actionable variants, including *BRCA1/2*, and variants in other HR-DDR genes, like *ATM*, which are of particular interest because of reported clinical trials enrolling PC patients carrier of PVs in these genes.

Milestone 2. PVs in other actionable genes (i.e., high risk *CDKN2A*) are expected to be found on the basis of our previous analyses in unselected PC cases from our cohort. These patients and their relatives will be candidate for specific research surveillance programmes (for PC) or established screening protocols for hereditary cancer syndromes and related cancers, according to the specific mutated genes.
Milestone 3. Overall, the combination of germline testing along with tumor mutational assessment will help discern the clinical relevance of deleterious variants and VUS in candidate genes and guide future therapeutic decisions, moving forward individualized patient care.

Figure 1. Algorithm of multiple-gene germline testing



MMR genes: *MLH1, MSH2, MSH6, PMS2, EPCAM*

9. References and relevant publications by the research group, already available

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PERSONNEL INVOLVED IN THE RESEARCH

Name and date of birth	Role on Project	Fellowship required	Effort on project (%)	Present position
1. Paola Ghiorzo (05.09.1970)	PI	NO	40%	Molecular Geneticist
3. M.Stefania Sciallero (22.11.1959)	Medical Oncologist Sub-Inv	NO	40%	Medical Oncologist
4. Alberto Puccini (29.07.1991)	Medical Oncologist Sub-Inv	NO	40%	Medical Oncology Fellow
5. Maria Laura Iaia (04.10.1987)	Medical Oncologist Sub-Inv	NO	40%	Medical Oncology Fellow
6. Roberto Borea (02.02.1992)	Medical Oncologist Sub-Inv	NO	40%	Medical Oncology Fellow
7. Linda Battistuzzi (26.11.1969)	Bioethicist Sub-Inv	NO	20%	Researcher
8. Federica Grillo (22.08.1974)	Pathologist Sub-Inv	NO	20%	Pathologist Researcher
9. Bruna Dalmasso (24.03.1983)	Medical Resarcher Sub-Inv	NO	20%	PhD candidate
10. Irene Vanni (05.12.1985)	Molecular Biologist Sub-Inv	NO	20%	PhD fellow
11. William Bruno (08.09.1976)	Medical geneticist Sub-Inv	NO	20%	Researcher
12. TBD	Biologist Sub-Inv	NO	100%	Fellow

DESCRIPTION OF THE WORK FOR EVERY UNIT OF PERSONNEL

Unit 1 will coordinate the project, plan experiments and evaluate results in close connection with leading Oncologist (Unit2),Unit -2-3-4-5 (Medical Oncologist and Medical Oncology Fellows). They will select and enrol in the study all consecutive new pancreatic cancer patients referred to the Medical Oncology Units at Policlinico San Martino IRCCS. They will properly inform the patients about the study protocol and, whether they accept, they will obtain their consent to participate. In addition, they will administer an “ad hoc” family history validated questionnaire to all patients. They will be responsible of treatment of the patients. They will collect outcome as well as translational research data, compiling a database which will serve for analyses. Unit 6, expert bioethicist, will deal with bioethical issues and clearance from Ethical Committee. Unit 7 , expert pathologist, will be in charge of selecting PC tissue for molecular analysis and IHC . Unit 8 and 9, PhD students, will

perfom data analysis and NGS design and planning, respectively . Unit10, experienced medical oncogenethicist , will perform genetic counselling . Unit 11, to be determined (TND) personnel, will be in charge of DNA extraction and NGS analysis. The projects benefits of young talented and already expert collaborators, as documented by the group relevant publications.

Budget Form /year

1. Research costs 43400 Euro
2. Instruments
3. Indirect costs
4. Sub-total 43400 Euro

5. Overheads 2170 Euro
6. Fellowships 25000 Euro

7. Total 70570 Euro

Justifications Itemized research costs Gene panel testing costs 240E per sample. We plan to test 160 samples (100 restrospective+60 prospective) for a total of 38400E. Additional DNA extraction from tissue, IHC and LOH analysis in selected case will be performed for a total of 5000E. The project would benefit of a one-year renewal.

EXISTING/PENDING SUPPORT None

SUGGESTED REVIEWERS (MAX 3)
Maurizio Genuardi maurizio.genuardi@unicatt.it (Università Cattolica del Sacro Cuore, Roma)
Sara Lonardi sara.lonardi@iov.veneto.it (Oncologia Medica 1, IOV Padova)
Matteo Fassan matteo.fassan@gmail.com (Anatomia Patologica, IOV Padova)

BIOETHICAL REQUIREMENT

1. Human experimentation ……(YES) – please provide clearance from the competent ethical committee as addendum A

2. Animal experimentation ….. (NOT) – please include a statement as addendum B specifying which regulations the proposed research meets

Declaration I shall confirm to the Declaration of Helsinki in its latest version. I shall also apply the Bioethics Convention of the Council of Europe. In implementing the proposed research, I shall adhere most strictly to all existing ethical and safety provisions applicable. Before start of the research, I shall obtain clearance from the competent ethical committee in case of involvement of human subjects in the research and /or in case of other ethical implications. I shall conform with all regulations protecting the animals used for research purpose.

Date: 17/02/2020 Name of PI Paola Ghiorzo Principal investigator's signature ……

……..

Authorized Administrative Official's signature…….. Date

Si autorizza al trattamento dei dati ai sensi del d.lgs. 196/2003