Q9

**From:** [redacted]
**Sent:** 22 December 2016 10:44
**To:** [redacted]
**Cc:**
**Subject:** Precision Medicine Ecosystem - Multiple Sclerosis - request for review

Dear [redacted]

The Scottish Government recently announced a £4 million investment in a Precision Medicine Ecosystem

http://news.scotland.gov.uk/News/Investing-in-the-healthcare-of-the-future-2255.aspx

The aim of this investment is to secure a fully integrated precision medicine platform that will "join up" the broad field of informatics to link detailed biology with human health and disease across Scotland.

An integral part of the Precision Medicine Ecosystem is the funding of 2 major exemplar projects. One of these is in the area of Multiple Sclerosis (*Future-MS*)

The principal aim of *Future-MS* is to build an integrated and comprehensive dataset that combines clinical, imaging, genomic, health and lifestyle data using a Scottish informatics platform

[redacted] from Edinburgh's Centre for Clinical brain Sciences was invited to submit the *Future-MS* proposal for review. We now seek to obtain independent expert opinion on the feasibility, appropriateness and value for money of the submitted proposal. The Scottish Government is minded to fund a version of *Future-MS*. We are very keen to maximise the impact of our investment and are therefore looking to international experts to provide critical feedback at this stage.

We would be very grateful to have your expert opinion on this application as an external referee. An anonymised copy of your comments will be fed back to the applicants.

I have attached a copy of the proposal and our standard external reviewer form.

If you are able to provide a review, could I ask that you return the completed review form to myself by Friday 27th January.

Kind regards

[redacted]

[redacted]
**Scottish Government Chief Scientist Office**
[redacted]
http://www.cso.scot.nhs.uk/

PME_FutureMS_... External Project Evaluation Fo...

**From:** [redacted]
**Sent:** 22 December 2016 10:39
**To:** [redacted]
**Cc:** [redacted]
**Subject:** Precision Medicine Ecosystem - Multiple Sclerosis - request for review

Dear [redacted]

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http://news.scotland.gov.uk/News/Investing-in-the-healthcare-of-the-future-2255.aspx

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[redacted]

[redacted]
**Scottish Government Chief Scientist Office**
[redacted]
http://www.cso.scot.nhs.uk/

External Project Evaluation Fo...

PME_FutureMS_...

**From:** [redacted]
**Sent:** 22 December 2016 10:55
**To:** [redacted]
**Cc:** [redacted]
**Subject:** Precision Medicine Ecosystem - Multiple Sclerosis - request for review

Dear [redacted]

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Kind regards

[redacted]

[redacted]
**Scottish Government Chief Scientist Office**

[redacted]
http://www.cso.scot.nhs.uk/

PME_FutureMS_... External Project Evaluation Fo...

**From:** [redacted]
**Sent:** 22 December 2016 10:50
**To:** [redacted]
**Cc:** [redacted]
**Subject:** Precision Medicine Ecosystem - Multiple Sclerosis - request for review

Dea[redacted]

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[redacted]

[redacted]
**Scottish Government Chief Scientist Office**
[redacted]
http://www.cso.scot.nhs.uk/

PME_FutureMS_... External Project Evaluation Fo...

**From:** [redacted]
**Sent:** 26 October 2016 15:18
**To:** [redacted]
**Cc:** Elsdon M (Mark).
**Subject:** Precision Medicine Programme - Pancreatic Cancer - request for review

Dear [redacted]

The Scottish Government recently announced a £4 million investment in a Precision Medicine Ecosystem

http://news.scotland.gov.uk/News/Investing-in-the-healthcare-of-the-future-2255.aspx

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An integral part of the Precision Medicine Ecosystem is the funding of 2 major exemplar projects. One of these is in the area of pancreatic cancer.

The main aim of *PRECISION-Panc* is to use genomic screening to "find the trial for the patient" and match the best new treatment options for an individual based on the molecular subtype of their cancer.

[redacted] from Glasgow's [redacted] Cancer Research Centre was invited to submit a proposal for *PRECISION-Panc* for review. We now seek to obtain independent expert opinion on the feasibility, appropriateness and value for money of the submitted proposal. The Scottish Government is minded to fund a version of *PRECISION-Panc*. We are, however, very keen to maximise the impact of our investment and are therefore looking to international experts to provide critical feedback at this stage.

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I have attached a copy of the proposal and our standard external reviewer form.

If you are able to provide a review, could I ask that you return the completed review form to myself by Friday 25th November.

Kind regards

[redacted]

[redacted]
Scottish Government Chief Scientist Office

[redacted]
http://www.cso.scot.nhs.uk/

Precision Panc Exemplar - Sub...

External Project Evaluation Fo...

**From:** [redacted]
**Sent:** 26 October 2016 15:25
**To:** [redacted]
**Cc:** [redacted]
**Subject:** Precision Medicine Programme - Pancreatic Cancer - request for review

Dear [redacted]

The Scottish Government recently announced a £4 million investment in a Precision Medicine Ecosystem

http://news.scotland.gov.uk/News/Investing-in-the-healthcare-of-the-future-2255.aspx

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Kind regards

[redacted]

[redacted]
Scottish Government Chief Scientist Office

[redacted]
http://www.cso.scot.nhs.uk/

Precision Panc Exemplar - Sub...

External Project Evaluation Fo...

**From:** [redacted]
**Sent:** 26 October 2016 15:02
**To:** [redacted]
**Cc:**
**Subject:** Precision Medicine Programme - Pancreatic Cancer - request for review

Dear [redacted]

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http://news.scotland.gov.uk/News/Investing-in-the-healthcare-of-the-future-2255.aspx

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Kind regards

[redacted]

[redacted]
Scottish Government Chief Scientist Office

[redacted]
http://www.cso.scot.nhs.uk/

External Project Evaluation Fo...

Precision Panc
Exemplar - Sub...

**From:** [redacted]
**Sent:** 26 October 2016 15:09
**To:** [redacted]
**Cc:**
**Subject:** Precision Medicine Programme - Pancreatic Cancer - request for review

Dear [redacted]

The Scottish Government recently announced a £4 million investment in a Precision Medicine Ecosystem

http://news.scotland.gov.uk/News/Investing-in-the-healthcare-of-the-future-2255.aspx

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If you are able to provide a review, could I ask that you return the completed review form to myself by Friday 25th November.

Kind regards

[redacted]

[redacted]
Scottish Government Chief Scientist Office

[redacted]
http://www.cso.scot.nhs.uk/

Precision Panc Exemplar - Sub...

External Project Evaluation Fo...

**From:** [redacted]
**Sent:** 26 October 2016 15:14
**To:** [redacted]
**Cc:** [redacted]
**Subject:** Precision Medicine Programme - Pancreatic Cancer - request for review

Dear [redacted]

The Scottish Government recently announced a £4 million investment in a Precision Medicine Ecosystem

http://news.scotland.gov.uk/News/Investing-in-the-healthcare-of-the-future-2255.aspx

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If you are able to provide a review, could I ask that you return the completed review form to myself by Friday 25th November.

Kind regards

[redacted]

[redacted]
Scottish Government Chief Scientist Office

[redacted]
http://www.cso.scot.nhs.uk/

Precision Panc Exemplar - Sub...

External Project Evaluation Fo...

**From:** [redacted]
**Sent:** 07 December 2016 13:53
**To:** [redacted]
**Cc:**
**Subject:** RE: Precision Medicine Programme - Pancreatic Cancer - request for review
**Attachments:** External Project Evaluation Form - Full Grant - TCS.docx

Dear [redacted] please find attached my comments relative to the application
Best Wishes
[redacted]

---

**From:** [redacted]
**Sent:** 26 October 2016 15:09
**To:** [redacted]
**Cc:** [redacted]
**Subject:** Precision Medicine Programme - Pancreatic Cancer - request for review

Dear [redacted]

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Kind regards

[redacted]

[redacted]
Scottish Government Chief Scientist Office

[redacted]
http://www.cso.scot.nhs.uk/

**********

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Tha am post-d seo (agus faidhle neo ceanglan còmhla ris) dhan neach neo luchd-ainmichte a-mhàin. Chan eil e ceadaichte a chleachdadh ann an dòigh sam bith, a' toirt a-steach còraichean, foillseachadh neo sgaoileadh, gun chead. Ma 's e is gun d'fhuair sibh seo le gun fhiosd', bu choir cur às dhan phost-d agus lethbhreac sam bith air an t-siostam agaibh, leig fios chun neach a sgaoil am post-d gun dàil.

Dh'fhaodadh gum bi teachdaireachd sam bith bho Riaghaltas na h-Alba air a chlàradh neo air a sgrùdadh airson dearbhadh gu bheil an siostam ag obair gu h-èifeachdach neo airson adhbhar laghail eile. Dh'fhaodadh nach eil beachdan anns a' phost-d seo co-ionann ri beachdan Riaghaltas na h-Alba.

**********

The Institute of Cancer Research: Royal Cancer Hospital, a charitable Company Limited by Guarantee, Registered in England under Company No. 534147 with its Registered Office at 123 Old Brompton Road, London SW7 3RP.

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CHIEF SCIENTIST OFFICE

Scottish Government
Riaghaltas na h-Alba
gov.scot

## Project Evaluation Form

| | |
|---|---|
| Project Reference: | Precision-Panc |
| Reviewer: | [REDACTED] |

**PLEASE NOTE THAT ANONYMISED COMMENTS MAY BE FED BACK TO THE APPLICANTS**

To help us, it would be useful if you would make your anonymised comments on page 2 in the following categories (**please do not write comments on this page**):

**1. Importance**

Please comment on the originality, relevance, implementability and potential impact of the proposed project.

**2. Methods**

Please comment on the appropriateness, rigour, and feasibility of the methods.

**3. Value for money**

Please comment on whether the cost of the research is justified by the potential importance of the findings.

**4. Modifications**

Please indicate any changes that might improve the research.

**5. Scoring Guideline**

| | |
|---|---|
| • Reject | 0 - 1 |
| • Major modification required | 2 - 3 |
| • Fund with minor modification | 4 - 5 |
| • Fund without modification | 6 |

Please write in score: [ 6 ]

ANONYMISED COMMENTS

Please feel free to comment on any aspect of this proposal

## 1. Importance

Very strong application by an outstanding team of clinicians and scientists with knowledge and skills across different disciplines applied to pancreatic cancer research

## 2. Methods

Strong rationale to support the integration of genomic data into a clinically applicable network and pipeline.

## 3. Value for money

The budget requested appears proportionate to the resources needed.

## 4. Modifications

none

Please return by email to: *[REDACTED]*

**From:** [redacted]
**Sent:** 23 November 2016 14:04
**To:** [redacted]
**Cc:**
**Subject:** SMS-IC PME - Future MS Exemplar for Peer Review
**Attachments:** PME_FutureMS_Final.pdf

[ Comment like attached was proposed. ]

Hi [redacted]

With apologies for the delay, please find attached for peer review the proposal for utilisation of CSO PME funding for the Future MS exemplar project.

If you need any further details, please let me know.

Kind regards, [redacted]

**Chief Scientist Office**

**1. Title:** *Precision Panc Infrastructure: Investing in the advancement of precision medicine in Scotland*

**2. Principal applicant, Institution and email address:** *Professor Andrew Biankin, University of Glasgow, [REDACTED]*

**3. Co-applicants(s) and Institution(s): N/A**

**4. Duration of project and total funding requested from CSO:** *6 months; £650,000.*

**5. Lay summary:**

Pancreatic cancer is currently the 4th, and will soon become the 2nd leading cause of cancer death in Western societies. Current treatments work only in a small fraction of people, and most live for only 6 months after their diagnosis, and almost all will die within a year. The problem is that the cancer in one patient is different to the cancer in another, and a "one size fits all" approach isn't working. The main aim of *PRECISION-Panc* is to use the latest technology to "find the trial for the patient" and match the best new treatment options for an individual based on the genetic subtype of their cancer.

**6. How will the proposed project demonstrate the Precision Medicine Ecosystem core ambition of *bringing Precision Medicine into Practice.***

The Vision of PRECISION-Panc is to accelerate the evolution of pancreatic cancer treatment into the molecular age of oncology, so that biopsy and molecular phenotype directed care and therapeutic development is part of routine clinical practice, which enhances scientific discovery, and continuously improves outcomes.

As a Precision Medicine Ecosystem exemplar project, the Precision Panc initiative will provide the following benefits:

- Improved patient outcomes in Scotland and elsewhere
- Enhanced inward flow to Scotland of Clinical Research with associated funding
- Places Scotland at the centre of a network of world class research in pancreatic cancer
- Supports the building of the Scottish Precision Medicine Ecosystem

Pancreatic ductal adenocarcinoma (PDAC) has one of the worst outcomes of any cancer, with a 5-year survival of less than 5%, and this continues to remain unchanged for almost 50 years [1]. It persists as the 4th, and will soon become the 2nd leading cause of cancer death in our society [2](it has recently overtaken breast cancer to be the third leading cause in the United States). Only ~15% of patients can have the cancer surgically extirpated, and even then, 80% die within 5 years. The majority present with advanced disease, with the standard of care for many years, Gemcitabine monotherapy, providing only a marginal survival advantage [3]. Further incremental improvements are possible with addition of Erlotinib [4] or Capecitabine [5], however, the survival benefit is measured in days or weeks, with the overall median still ~6 months. More recently, Gemcitabine + *nab*-Paclitaxel [6] and *FOLFIRINOX* combinations [7, 8] have become the standard of care for patients with good performance status, but only extend survival by a meagre 2.5 and 5 months, to 8.5 and 11 months respectively. However, the 2-year survival for advanced disease remains less than 7%. Intriguingly, minor subgroups of patients, who cannot as yet be identified a-priori, derive significant benefit from some of these therapies.

The elucidation of molecular diversity within previously indistinguishable cancer types has created significant opportunities to improve patient outcomes using agents that target specific molecular mechanisms. The need to effectively test and deliver such precision oncology approaches has seen the creation of broad based programmes for many cancer types, e.g. NCI-MATCH; CRUK-SMP, SpectaCOLOR and SpectaLUNG. The overarching objective of the assembled team is to establish a stratified therapeutic development platform for pancreatic cancer, as one does not exist in the UK, and multiplex molecular assays appropriate to PDAC are not available. Based on emerging data for PDAC, particularly concerning its diversity with regard to "actionable vulnerabilities", there is a clear need to better match patients to specific therapies based on molecular phenotype to appropriately test and then apply them in the clinic.

*PRECISION-Panc* is a synergistic and dynamic platform aligning and coordinating pre-clinical discovery and clinical development. The ultimate goal is to offer every pancreatic cancer patient molecular profiling with a viable and attractive clinical trial option; to find *"the trial for the patient"*, rather than *"the patient for the trial"*; create opportunities for scientific research that were previously intractable, and enable forward and backward translation between the laboratory and the clinic (Biankin *et al.* Nature 2015) [9]. There is extensive and broad support for *PRECISION-Panc* as it is now well-recognised that this type of approach is absolutely necessary in order to make more than just incremental progress. The Pancreas Cancer sub-group of the NCRI Upper GI Cancer Clinical Study Group is actively contributing to trial design and is fully "on-board" with access to thousands of potential participants through the network (please see letter from [REDACTED]).

Similarly, the CRUK Glasgow Clinical Trials Unit (CTU) is central to the development and implementation of *PRECISION-Panc*, and this is a central focus of their activity (see letter of support from CTU Director Rob Jones). As a consequence, the final trial designs have been examined and modified by over 20 clinical trial experts across the UK to arrive at final designs. Further vigorous support for *PRECISION-Panc* comes from industry, with significant co-investment from Celgene of ~$5 million US to contribute to this proposal (see letter of support). Other letters of support from the pharmaceutical industry are appended. Significant UK-wide and Scotland-based programmes have also invested in *PRECISION-Panc*. They make it clear that without such a programme as *PRECISION-Panc*, it is currently impossible to develop many therapies in pancreatic cancer. This creates scope for additional industry investment in the UK, which is important given that industry investment, particularly in the healthcare sector, is diminishing.

A proposal requesting ~£10 million is under the late stages of consideration at Cancer Research UK. The Precision Medicine CATAPULT has named *PRECISION-Panc* as an exemplar project and is providing significant financial and strategic support. The Scottish Genomes Partnership (aligned and partnered with Genomics England) is also lending capacity and resources toward *PRECISION-Panc*. Biankin is the co-PI for a programme called Precision Promise, the US version of *PRECISION-Panc*, which is a US $33 million investment by the Pancreatic Cancer Action Network. Precision Promise is entirely complementary to *PRECISION-Panc* and aligned to accelerate therapeutic development for pancreatic cancer (see letter from [REDACTED], [REDACTED] of Pancreatic Cancer Action Network). The main driver for this approach is the clear need to screen more patients and test therapies that are likely to be efficacious in small subgroups, and this will require large networks that provide composite datasets

to support efficacy of a specific therapeutic strategy. Patients and advocacy groups such as Pancreatic Cancer UK view the *PRECISION-Panc* strategy as a priority. Pancreatic Cancer UK and their advocates have been involved in the development of patient information sheets, consent forms and the website for *Precision-Panc*, and will play a key role in patient and clinician awareness of *PRECISION-Panc* in order to further enhance participation (see letter from Pancreatic Cancer UK). In addition, individual interviews with *PRECISION-Panc* patient representatives and focus groups have identified that "finding the trial for the patient" is key to increasing clinical trial recruitment by offering attractive options to all patients.

Moreover, our In-House Trial Advisory Board (IHTAB) at the Glasgow CTU has strong patient representation and involvement. With this weight of support from all sectors, and initial financial investment to start to build this infrastructure, it is overtly clear that *PRECISION-Panc* is what is required in order to accelerate therapeutic development and scientific discovery for pancreatic cancer. The concept is strong and is being implemented in other cancers, and in other countries for pancreatic cancer – which on the whole is driven by the leadership of this proposal.

As a consequence, *PRECISION-Panc* will be part of a GLOBAL network, which will streamline data sharing, coordination, standardisation and harmonisation of approaches to accelerate precision medicine strategies for pancreatic cancer. The team and its established partners bring together investigators from the foremost cancer centres in the UK, with multidisciplinary expertise in oncology, cancer genomics, cancer biology, cancer immunology, pharmacology, experimental medicine, clinical trials, and computational bioinformatics. It builds on their international standing in the field with recent examples including publications in *Nature* [9-15], *Cell* [16, 17], *Cancer Cell* [18, 19] and other major high impact journals that include reports as members of international expert consensus and classification committees [20-28]. We are a multidisciplinary team that encompasses the essential areas that are required, with the leadership team consisting of 2 medical oncologists, a surgical oncologist and a basic scientist. Individual members, or external parties, can propose and lead trials to utilise *PRECISION-Panc* molecular capacity, with existing trials such as SIEGE, SCALOP2, PIONEER and ESPAC5, and existing industry sponsored studies (e.g. Halozyme) already engaged with the platform with plans to integrate workflows over time. As every patient has a tumour biopsy, we can relate findings from the trials performed to molecular characteristics of the tumour and the patient.

Our studies have identified defects in DNA damage response (DDR) as a critical Achilles heel in pancreatic cancer. This was highlighted as the most significant opportunity for improving outcomes at the recent American Association of Cancer Research (AACR) Pancreas Meeting in Orlando, and once again at Pancreas 2016 in Glasgow in June. We will leverage clinical trials to exploit this vulnerability in relevant patient subsets, including refining predictive correlates of response to agents that target DDR deficiency. In addition, based on exciting new data, we will investigate opportunities for therapies that target the immune system. Our robust clinical enterprise will be integrated with pre-clinical pipelines incorporating and standardising relevant *in vitro* and *in vivo* approaches (e.g. organoids, tissue explants, patient-derived xenografts/cell lines, and genetically engineered mouse models). These will enable mechanistic insights into molecularly defined therapeutic vulnerabilities in pancreatic cancer, including immunotherapy, and how these might relate to the DDR phenotype. We will also contribute to the next iteration of the International Cancer Genome Consortium (ICGC) -

known as the ICGC for medicine (ICGCmed) - where [REDACTED] plays a leadership role as part of the central steering committee.

The assembled team includes the ICGC Pancreatic Ductal Adenocarcinoma (PDAC) genomics team who have extensively characterised a large number of PDACs. These analyses reveal important biological insights, and are reported in seminal articles published in high profile journals [9-11, 15, 29]. These in depth analyses have uncovered an unprecedented level of detail of the molecular pathology of PDAC and candidate underlying vulnerabilities. Here we will focus on defects in the DNA damage response (DDR) pathway, apparent in ~20% of PDAC, and based on our most recent, and very exciting novel data, extend these investigations into overlapping vulnerabilities through targeting the immune system.

**7. Who will use the research findings and how will they be disseminated and used?**
Research results will be freely shared directly with the patient's primary health care team in the first instance. These results will be used to consider the whether standard therapy or an alternative therapy option would be more suitable for the patient. Larger scale datasets will be aggregated, analysed and results published in a peer-reviewed journal.

**8. Research plan**
PRECISION-Panc aims to accelerate scientific discovery through the coordination of world-leading pancreatic cancer research. The mission is to identify, test and then implement stratified therapeutic approaches that will improve overall outcomes for patients. [REDACTED], [REDACTED] of Surgery and Director Wolfson Wohl Cancer Research Centre, Glasgow leads the study. The initiative is structured as a consortium of approximately 100 clinical and research members from across five CRUK centres (Glasgow, Manchester, Cambridge, Oxford and London).

The project is intended primarily to characterise rapidly an individual patient's pancreatic cancer and introduce each to the appropriate one of a number of available clinical trials designed to treat that specific tumour type. In this way recruitment to clinical trials is rendered much more efficient with consequent reduction is costly up front expenditure on screening. This can be viewed as a valuable service to patients who have an enhanced option to be treated early with novel therapeutic agents and also as a valuable service to the research community and to commercial drug developers who are willing to pay enhanced Clinical Trials fees in return for assured patient recruitment in this challenging area. The overall investment in PRECISION-Panc is of the order of £ 20 million.

Proposed Workflows

1. Previously diagnosed Pancreatic Cancer patients will be referred to PP and entered into an umbrella clinical trial protocol (PRIMUS)
2. A tumour biopsy is shipped to PRECISION-Panc
3. Tissue sample is logged, labelled and tracked through the process
4. DNA is extracted and genomic screening is conducted in parallel with other laboratory assessments to fully characterise the tumour
5. PP Multi-Disciplinary Molecular Diagnostic Team assesses the patient and recommends action to be taken:
    a. Entry into appropriate clinical trial in Scotland
    b. Entry into appropriate clinical trial ex-Scotland

c. Continue with existing Standard of Care

Whilst it continues to be refined (and regulated) for use in precision medicine, genomic sequencing is routinely used to direct clinical decision making in many parts of the world already. However, in addition to strengthening the link between the care provided by the National Health Service and research activities, further key areas that must be rapidly developed in order to fully implement precision medicine in Scotland include infrastructure, logistics, data collection, sharing and storage. Overall, the aim is to combine *genetic* data with *patient* data to identify the most suitable therapeutic option for the patient. This is a massive undertaking – it includes integration and interpretation of "-omic" molecular data with research data, patient phenotypic data and follow up in order generate a patient report that can be recorded within the patient's electronic health record. The reliability and robustness of the interpretation of these combined datasets, to provide the aforementioned guidance, is entirely dependent on the quality of the data upon which that interpretation is based.

***Scottish PME contribution***

This application requests support from the PME for the following key areas:

1. Patient/sample/data tracking infrastructure
2. Laboratory Information Management System (LIMS)
3. High throughput validation and testing of genomic platforms

Over the past 16 months, we have been exploring the clinical journey of the typical pancreatic cancer patient in order to understand the various checkpoints where data is collated and decisions are made. Clearly there is a wealth of patient-specific data held within the NHS that ideally should be melded with the genomic data generated for that patient. However, much of this phenotypic patient data is unstructured and is held an array of formats (word-based, PDF, hospital specific systems etc). This can inhibits the ability to track the patient journey seamlessly, making the collection and interpretation of data to form a knowledge-base for future learning somewhat challenging.

Over the past year, we have cultivated relationships with the local e-Health Leads at Greater Glasgow and Clyde NHS, Orion Healthcare, NHS Biorepositories, Aridhia and Stratified Medicine Scotland in order to develop a prototype to track patients and the samples associated with them. These interactions have been fruitful and the shared kernels of knowledge have generated a clear overview of what is required. As part of SMS-IC, Aridhia developed systems to hold existing research data generated by the pancreatic research community, a prototype decision support tool for use by the molecular Multi-Disciplinary Team and a prototype administration & tracking system for research participants and diagnostic service customers.

Our current systems are rudimentary in nature and require intensive further development, testing and integration with other systems in order to further develop systems which facilitate the sharing of data in, or as close to, real time as possible.

In order to allow clear and transparent tracking of patients and their samples through the study, we request the support of a software developer over three years to work closely with us and with these

wider groups to fully develop a system to enable real-time patient, data and sample tracking throughout all aspects of the Precision Panc study.

The precision medicine laboratory at the [REDACTED] Cancer Research Centre has established the initial infrastructure and sequencing capabilities to perform a wide range of genomic assays on both normal and disease states. We can now deliver at low scale assays that encompass panel assessment and whole genome sequencing as well as RNA seq. Whilst we can deliver these assays on an individual and small-scale basis, the challenge is now to automate, scale and achieve regulatory approval of the laboratory in order to deliver these assays to the clinic.

This is an essential component of what the precision medicine laboratory aims to deliver for the Precision Medicine Ecosystem and Scottish Genomes Partnership as well as individual projects such as Precision Panc and the Ovarian Cancer Project. The laboratory will deliver assays for specific programmes across the UK, and is positioning itself to deliver assays to the people of Scotland through the NHS. These efforts are in partnership with the Stratified Medicine Scotland Innovation Centre, the Scottish Genomes Partnership, and major universities in Scotland. These are all under the umbrella of the Precision Medicine Ecosystem, and integrate with the NHS through activities within the Precision Medicine Ecosystem, and coordinate with other NHS wide activities such as Digital Health.

A central requirement of the laboratory is to deliver these reproducible assays that are robust and clinically validated in conjunction with reproducible analytics. This requires a significant investment in the workflows that stem from the point of sample acquisition, to sample tracking including analyte processing, to sequencing right through to delivery of a molecular report for each individual patient. The next stage of implementation involves testing our systems in real time, using samples provided from the local NHS biorepository consented for research purposes, to demonstrate reproducibility at high throughput and thus provide the details and proof of system robustness required prior to the project launching formally.

A further key element, and an element without which the laboratory can function at scale, is a laboratory information management system (LIMS). This system enables the tracking of samples as they enter the laboratory so there are no sample mix-ups, and that each biospecimen or biospecimen-derived analyte is accounted for and a wide range of metadata is tracked and stored for audit purposes. This is of fundamental importance, without which the laboratory cannot progress to the scale, robustness and quality required for regulatory approval, and as a consequence delivery of pre-sequences to patients and return of results to inform clinical trials selection of patient management.

The Laboratory Management Information System (LIMS) will electronically track & record the following:

- Will allow collaborators to enter in sample/patient data directly into the LIMS
- Patient anonymisation
- Will allow an automatic dispatch alert system and receipt reports
- Sample and reagent expiry warnings
- Patient consent tracking, linked to the relevant specimen, samples, blocks and slides which can then be queried/listed and quarantined
- Audit reports i.e. Chain of custody reports with electronic signatures

- Ability to print labels for pathology cassettes, tubes and slide labels with user defined and customisable fields
- Fridge & freezer tracking
- Sample tracking to monitor volumes and usage
- Workflow data retention i.e. protocol or kit used, and any changes to the protocol
- Patient specimen and derivatives tracking
- Sample data aggregated and attached to specimen or patient ID
- Electronic transfer of all relevant data directly to the Sequencing Clarity LIMS system.

To maximise this investment, we also request the support of a LIMS/Software Developer who can develop the Laboratory Management Information System in a manner to deliver automation within and between each of the workflow steps.

**9. References**


1. Vogelzang NJ, Benowitz SI, Adams S, et al. Clinical cancer advances 2011: Annual Report on Progress Against Cancer from the American Society of Clinical Oncology. J Clin Oncol 2012;30:88-109.
2. Rahib L, Smith BD, Aizenberg R, et al. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. Cancer Res 2014;74:2913-21.
3. Burris HA, Moore MJ, Anderson J, et al. Improvements in survival and clinical benefit with Gemcitabine as first-line therapy for patients with advanced pancreas cancer: A randomised trial. J Clin Oncol. 1997;15:2403-2413.
4. Moore MJ, Goldstein D, Hamm J, et al. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 2007;25:1960-6.
5. Cunningham D, Chau I, Stocken DD, et al. Phase III randomized comparison of gemcitabine versus gemcitabine plus capecitabine in patients with advanced pancreatic cancer. J Clin Oncol 2009;27:5513-8.
6. Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med 2013;369:1691-703.
7. Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 2011;364:1817-25.
8. Gourgou-Bourgade S, Bascoul-Mollevi C, Desseigne F, et al. Impact of FOLFIRINOX Compared With Gemcitabine on Quality of Life in Patients With Metastatic Pancreatic Cancer: Results From the PRODIGE 4/ACCORD 11 Randomized Trial. J Clin Oncol doi:10.1200/JCO.2012.44.4869 2012.
9. Bailey P, Chang DK, Nones K, et al. Genomic analyses identify molecular subtypes of pancreatic cancer. Nature 2016;531:47-52.
10. Hudson TJ, Anderson W, Aretz A, et al. International network of cancer genome projects. Nature 2010;464:993-998.
11. Biankin AV, Waddell N, Kassahn KS, et al. Pancreatic cancer genomes reveal aberrations in axon guidance pathway genes. Nature 2012;491:399-405.

12. Perez-Mancera PA, Rust AG, van der Weyden L, et al. The deubiquitinase USP9X suppresses pancreatic ductal adenocarcinoma. Nature 2012;486:266-70.
13. Alexandrov LB, Nik-Zainal S, Wedge DC, et al. Signatures of mutational processes in human cancer. Nature 2013;500:415-21.
14. Biankin AV, Piantadosi S, Hollingsworth SJ. Patient-centric trials for therapeutic development in precision oncology. Nature 2015;526:361-70.
15. Waddell N, Pajic M, Patch AM, et al. Whole genomes redefine the mutational landscape of pancreatic cancer. Nature 2015;518:495-501.
16. Weissmueller S, Manchado E, Saborowski M, et al. Mutant p53 drives pancreatic cancer metastasis through cell-autonomous PDGF receptor beta signaling. Cell 2014;157:382-94.
17. Tape CJ, Ling S, Dimitriadi M, et al. Oncogenic KRAS Regulates Tumor Cell Signaling via Stromal Reciprocation. Cell 2016;165:910-20.
18. Biankin AV, Maitra A. Subtyping Pancreatic Cancer. Cancer Cell 2015;28:411-3.
19. Steele CW, Karim SA, Leach JD, et al. CXCR2 Inhibition Profoundly Suppresses Metastases and Augments Immunotherapy in Pancreatic Ductal Adenocarcinoma. Cancer Cell 2016;29:832-45.
20. Morran DC, Wu J, Jamieson NB, et al. Targeting mTOR dependency in pancreatic cancer. Gut 2014;63:1481-9.
21. Basturk O, Hong SM, Wood LD, et al. A Revised Classification System and Recommendations From the Baltimore Consensus Meeting for Neoplastic Precursor Lesions in the Pancreas. Am J Surg Pathol 2015;39:1730-41.
22. Carlino MS, Kwan V, Miller DK, et al. New RAS-mutant pancreatic adenocarcinoma with combined BRAF and MEK inhibition for metastatic melanoma. J Clin Oncol 2015;33:e52-6.
23. Chantrill LA, Nagrial AM, Watson C, et al. Precision Medicine for Advanced Pancreas Cancer: The Individualized Molecular Pancreatic Cancer Therapy (IMPaCT) Trial. Clin Cancer Res 2015;21:2029-37.
24. Miller BW, Morton JP, Pinese M, et al. Targeting the LOX/hypoxia axis reverses many of the features that make pancreatic cancer deadly: inhibition of LOX abrogates metastasis and enhances drug efficacy. EMBO Mol Med 2015;7:1063-76.
25. Gingras MC, Covington KR, Chang DK, et al. Ampullary Cancers Harbor ELF3 Tumor Suppressor Gene Mutations and Exhibit Frequent WNT Dysregulation. Cell Rep 2016;14:907-19.
26. Kleeff J, Korc M, Apte M, et al. Pancreatic cancer. Nat Rev Dis Primers 2016;2:16022.
27. Martinelli P, Carrillo-de Santa Pau E, Cox T, et al. GATA6 regulates EMT and tumour dissemination, and is a marker of response to adjuvant chemotherapy in pancreatic cancer. Gut 2016.
28. Takaori K, Bassi C, Biankin A, et al. International Association of Pancreatology (IAP)/European Pancreatic Club (EPC) consensus review of guidelines for the treatment of pancreatic cancer. Pancreatology 2016;16:14-27.
29. Nones K, Waddell N, Song S, et al. Genome-wide DNA methylation patterns in pancreatic ductal adenocarcinoma reveal epigenetic deregulation of SLIT-ROBO, ITGA2 and MET signaling. Int J Cancer 2014.

**10. Justification of Resource**

£160,000 is requested to support the salary of a software engineer to specifically develop and engineer the processes to collect, collate and display data from a range of sources in order to track patients, their data and their samples within the NHS and research facilities involved in Precision Panc. A further £40,000 is requested to support compute, storage and software packages associated with this activity.

£337,355 is requested for the implementation and development of a Laboratory Information Management System (LIMS) that breaks down as follows (based on current quotation from supplier):

| StarLIMS | Costs |
|---|---|
| Full Concurrent User License | £53,231 |
| Framework Module | £6,161 |
| Mobile and HTML5 Designer License | £6,161 |
| Mobile User License | £1,232 |
| Mobile and HTML5 Configuration Training Course | £914 |
| Application Training Course | £4,005 |
| Configuration Training Course | £4,005 |
| Report Training Course | £2,710 |
| Consultation Service Package | £59,100 |
| Annual Maintenance Plan | £40,071 |
| LIMS Developer (3 yr) | £159,765 |

A further £112,618 is requested for the implementation, testing and validation of high throughput sequencing processes within the Precision Medicine Laboratory at the *[REDACTED]* Cancer Research Centre within the University of Glasgow. Samples will be retrieved from the Greater Glasgow and Clyde Biorepository, nucleic acids will be extracted before being subjected to library making and sequencing on the HiSeqX to verify robustness of the sequencing workflow at WWCRC as part of the plan to obtain ISO accreditation for these processes.

*The proposal should be completed using the headings provided and should be no longer than a total of 8 pages of text for **sections 1 to 10** completed in Calibri font at font size 11 with no changes to the line spacing or the margins of the form. Please delete this header and the guidance notes in the form.*

**Chief Scientist Office**

**1. Title:** FutureMS: Clinical, laboratory, and genomic predictors of disease activity in people with newly diagnosed relapsing-onset MS

**2. Principal applicant, Institution and email address:** [redacted] Centre for Clinical Brain Sciences, University of Edinburgh, [redacted]

**3. Co-applicants(s) and Institution(s):** *names of Co-applicants and Institutions (no email addresses needed)* [redacted] University of Edinburgh.

**4. Duration of project and total funding requested from CSO:** 9 months, £650K

**5. Lay summary:** Multiple Sclerosis is a chronic, incurable, and devastating disorder of the nervous system. It is the leading non-traumatic cause of acquired disability among young-adults in the industrialised world; 85% of the 2M+ prevalent cases are of working age, and Scotland has a disproportionate burden (>10K [c.0.2% population] prevalence, with the highest recorded global incidence in Orkney). Unlike other major neurological diseases such as Parkinson's or Alzheimer's, MS does not have a single and uniform "downward" disease trajectory. It is inherently unpredictable and variable. For example, some patients despite disease duration of over 15 years will, without treatment, experience a mild course with marginal disability whilst others are seriously disabled within a few years of diagnosis. Being able to predict individual disease course at the point of diagnosis is thus vital to allow informed life-choice and treatment decision making. The latter is particularly relevant to MS because, uniquely of the major neurological diseases, there are many potentially disease modifying treatments (DMTs) - with varying efficacy and risk - available for the newly diagnosed patient. And yet today, we are unable to reliably predict, at disease onset, if the individual will have mild, intermediate or severe disease course. This highlights the need for validated and quantitative precision medicine tools that will allow the reliable prediction of disease course at diagnosis. In order to achieve this long-term objective of FutureMS, there is a need to first build an integrated and comprehensive dataset that combines clinical, imaging, genomic, health and lifestyle data using a Scottish informatics platform. This incredibly valuable dataset will then allow the creation of rich datasets that plot the trajectory of individual patients and thus begins to allow associations with biological, imaging and clinical measures to be found. Over time, the "richness' of the data will only grow and through serial "mining", the aim is to build, test and validate predictive tools for newly diagnosed MS patients.

**6. How will the proposed project demonstrate the Precision Medicine Ecosystem core ambition of *bringing Precision Medicine into Practice.***

MS is in many ways the ideal disease to showcase Scottish capability in precision medicine innovation. The reasons include; disproportionate prevalence, a variable and unpredictable course, and many DMTs on the market with very different efficacy and risk profiles. Combined with quantitative surrogate markers of disease activity, it is ripe for integrated data mining to generate predictive tools – the goal of FutureMS. Such a "disease activity" prediction tool will inform physician-patient prospective decision-making about the personalised risk/benefit relationship of DMTs. From an economic viewpoint, the rapid inflation of MS DMT costs through evolution of the

available products and changes in prescribing practice represents a substantial challenge to NHS Scotland and all international healthcare funders. The need for therapeutic targeting through precision medicine is therefore urgent.

As a Precision Medicine Ecosystem exemplar project, FutureMS initiative will provide the following benefits:

- *Improving patient outcomes*: A 'deep dive' into the potential clinical, laboratory, and genomic predictors of disease activity at the individual-subject level, culminating in the formation of a prediction tool to allow for better care planning and prospective stratification
- *Global Exemplar Dataset*: A wholly unique cohort with the potential of finding novel observations mined from the deep phenotype dataset, a commercially attractive asset to the global pharma industry in its own right and as an offering for federated analysis
- *Enhanced inward flow of research funding for Clinical Research*: The creation of a long-term cohort that will continue to increase in value after the end of the initial study, presenting the means of rapid participant identification for clinical trials.
- *Reusable and Scalable Infrastructure*: Building a reusable national infrastructure (initially 4 nodes) with capability to capture deep phenotype patient data including; 'non-routine' patient data, linked NHS laboratory data, MRI imaging, and complex genomic profiling.
- *Brain Imaging Platform:* Building a Scottish-based imaging acquisition and analysis pipeline to build and develop neurological imaging intellectual property in Scotland, applicable to other disease areas.

**7. Who will use the research findings and how will they be disseminated and used?**

Research findings will be utilised by the FutureMS team to develop the prognostic toolset, this will have direct patient benefits, as well as having commercial potential for further exploitation. The Cohort dataset is a high-value commodity sought by the Pharma industry to mine for therapy developments programmes – access to such has already been agreed with Biogen in return for project funding, however there is interest from other corporations that can be exploited by appropriate means.

**8. Research plan**

This application requests support from the PME for the following key areas:

*1. Whole Genome Sequencing (WGS).* The ability to "upgrade" the FutureMS genomic dataset from single nucleotide polymorphism (SNP) based analysis to WGS is a major opportunity to leverage and futureproof FutureMS. Although the existing FutureMS genomic worskstream will bring novel and powerful value, WGS is state of the art and increasingly industry and academic standard compared to single nucleotide polymorphism (SNP) based analysis. WGS offers the most comprehensive method for analysing the genome, realising the unique opportunity to elucidate the genetic architecture of relapsing-remitting MS. Specifically, the value of WGS compared to planned SNP coverage is unbiased and finer resolution (>100x) of the entire genome compared to SNPs which are limited to common population variation and will also miss many potentially functionally important genetic variations such as repeats or deletions.

WGS will be undertaken by Edinburgh Genomics (EG). EG is the leading open access genomics and bioinformatics service provider in the UK and one of the largest sequencing facilities in Europe. EG is

based at the Roslin Institute with one sequencing technology platform, (Illumina HiSeq X Five) in a fully automated workflow, designed for high throughput WGS. The HiSeq X is the latest population-scale sequencing platform for any species, capable of delivering the equivalent of 1,800 human genomes at 30x coverage per instrument per year. This enables EG to produce very high quality data at unprecedented speed for around $1,000 per genome. The EG Facility runs Illumina's SeqLab end-to-end workflow solution, which seamlessly integrates the HiSeq X sequencers, Hamilton liquid handling robots and Genologics Clarity LIMS X system. Since start-up in late 2015, EG has sequenced over 4,500 complete genomes, largely human but also farm animals (swine, bovine, chicken, goat and sheep) plus dog, wildcat and water buffalo genomes. The addition of WGS data will futureproof and enhance the high value dataset that the FutureMS project is seeking to build. This aligns FutureMS with what competing studies are collecting and meets industry expectations. This enhanced dataset will be a key offering in SMS's goal of providing data and hosting federated datasets from other partners, providing a competitive offering of genomic data linked to a uniquely extensive clinical annotation dataset.

*2. Scottish brain imaging platform capability development.* Resilient quantitative image analysis pipelines are essential to the effective conduct of large-scale cohort studies such as FutureMS, which rely on neuroimaging endpoints. Despite similar major programmes being led from Edinburgh, and established local world class imaging expertise, MRI studies are currently being exported to other UK centres for analysis. This results in loss of data oversight, academic outputs, and significant income streams. We propose to develop additional image analysis capacity, through targeted recruitment of an imaging scientist, to support FutureMS in Edinburgh, leveraging extensive existing infrastructure and expertise within Imaging Sciences at Edinburgh University. This project will be led by [redacted] recently appointed Chair in Neuroradiology. The new appointment(s) will work within the existing image analysis group to develop, adapt, test and refine image processing and analysis pathways targeted to multiple sclerosis studies. The project will develop independent imaging analysis capacity to support and inform large scale multiple sclerosis research projects across Scotland. Furthermore, scalable and transferable cross-cutting imaging expertise and infrastructure will provide a scalable platform for deployment in other key neurological disease areas such as dementia, neurodegenerative disorders and neuro-oncology.

*3. Scottish precision medicine clinical research capacity development (neuroscience).* Development of a cohort of translational clinician scientists with requisite experience and skills will be pivotal to the successful creation of a Scottish Precision Medicine Ecosystem for translational medicine that is academically productive and that represents an attractive environment for inward investment. We propose recruitment of clinical research associate to be jointly supervised between Glasgow and Edinburgh in order to 'kick-start' build of this capacity and to further cement the links between Scotland's two largest clinical neuroscience research hubs. Together with the flat governance and organisational structure of FutureMS (linking NRS nodes at Aberdeen, Dundee, Edinburgh, and Glasgow), this will help realise the vision of Scotland operating as a 'single site' for Precision Medicine research in clinical neuroscience.

**9. References**

**10. Justification of Resource**

*Whole Genome Sequencing*

£375K: Samples to be sequenced by Edinburgh Genomics in 2 batches (100 & 300) using Illumina HiSeq X instruments, the current industry standard WGS units.

*Brain Imaging Acquisition and Analysis Platform*

£110K: To support a whole time early stage post-doctoral imaging scientist, and 0.25 WTE equivalent mid grade imaging scientist.

*Scottish precision medicine clinical research capacity*

£165,000: Requested for 'full economic costing' for an identified Clinical Research Fellow

**11. Expert referees**

[redacted]- Sheffield
[redacted]- San Raffaele, Italy
[redacted]- Bristol University
[redacted]- Cardiff University

**12. Declaration**

**Principal Applicant:** To my knowledge the project outline described here represents the ideas, concepts and writings of myself and co-investigators and is not a modification of projects submitted by others elsewhere.

| Signature of Principal Applicant | Name | Date |
|---|---|---|
| [redacted] | [redacted] | 23 November 2016 |

**Sponsor(s):** I agree to be sponsor/co-sponsor/joint sponsor (delete as appropriate) for this project under the requirements of the Research Governance Framework for Health and Community Care in Scotland.

| Signature *for and on behalf of the Sponsor Organisation(s)* | Name/Organisation | Date |
|---|---|---|
| | | |
| | | |

CHIEF SCIENTIST OFFICE

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## Project Evaluation Form

| | |
|---|---|
| Project Reference: | Future-MS |
| Reviewer: | [REDACTED] |

**PLEASE NOTE THAT ANONYMISED COMMENTS MAY BE FED BACK TO THE APPLICANTS**

To help us, it would be useful if you would make your anonymised comments on page 2 in the following categories (**please do not write comments on this page**):

**1. Importance**

Please comment on the originality, relevance, implementability and potential impact of the proposed project.

**2. Methods**

Please comment on the appropriateness, rigour, and feasibility of the methods.

**3. Value for money**

Please comment on whether the cost of the research is justified by the potential importance of the findings.

**4. Modifications**

Please indicate any changes that might improve the research.

**5. Scoring Guideline**

- Reject 0 - 1
- Major modification required 2 - 3
- Fund with minor modification 4 - 5
- Fund without modification 6

Please write in score: [ ]

ANONYMISED COMMENTS

Please feel free to comment on any aspect of this proposal

**1. Importance**

**2. Methods**

**3. Value for money**

**4. Modifications**

Please return by email to: [REDACTED]

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## Project Evaluation Form

| | |
|---|---|
| Project Reference: | Precision-Panc |
| Reviewer: | [REDACTED] |

**PLEASE NOTE THAT ANONYMISED COMMENTS MAY BE FED BACK TO THE APPLICANTS**

To help us, it would be useful if you would make your anonymised comments on page 2 in the following categories (**please do not write comments on this page**):

**1. Importance**

Please comment on the originality, relevance, implementability and potential impact of the proposed project.

**2. Methods**

Please comment on the appropriateness, rigour, and feasibility of the methods.

**3. Value for money**

Please comment on whether the cost of the research is justified by the potential importance of the findings.

**4. Modifications**

Please indicate any changes that might improve the research.

**5. Scoring Guideline**

- Reject 0 - 1
- Major modification required 2 - 3
- Fund with minor modification 4 - 5
- Fund without modification 6

Please write in score: [ ]

ANONYMISED COMMENTS

Please feel free to comment on any aspect of this proposal

**1. Importance**

**2. Methods**

**3. Value for money**

**4. Modifications**

Please return by email to: [REDACTED]